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The link between immunity, autoimmunity and endometriosis: a literature update

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ABSTRACT

Endometriosis (EMS), an estrogen-dependent inflammatory disorder affects approximately 5- 10% of the general female population of reproductive age and 20-90% of women with pelvic pain and infertility. Many immunological factors are known to contribute significantly to the pathogenesis and pathophysiology of EMS, and both chronic local inflammation and autoantibodies in EMS shares many similarities with autoimmune diseases (AD). However, the autoimmune etiology in EMS remains controversial, and its evidence on autoimmune basis may be limited. Here we aim to review the current understanding between autoimmunity and EMS to provide important knowledge to develop future potential immunomodulatory therapy for the treatment of EMS.

Keywords: Endometriosis (EMS), autoimmune disease (AD), autoantibodies, complement(C), cytokines, immune escape, immunomodulators

Introduction

Endometriosis (EMS), defined by the presence of endometrial glands and stroma outside the uterus, is a common chronic disease affecting up to 10% of the general female population of reproductive age (1,2) and 20-90% women with pelvic pain and infertility. Exacting prevalence in the population is difficult to determine because it is asymptomatic or subclinical in the majority of cases. Although its pathogenesis has not been completely identified, EMS has been characterized as an estrogen-dependent chronic inflammatory disease.(2-4) The most popular and widely accepted etiology is Sampson's theory of retrograde menstruation. (5) This theory describes how viable endometrial tissue can be spread into the peritoneal cavity through the fallopian tubes during menstruation eliciting an inflammatory response. This was further supported by finding showing women with EMS with greater volume of refluxed blood during menses than those without EMS. (6) Recent evidences suggest that the endocrine/paracrine influences and immunological aspects such as growth factors, cytokines, immune cells and hormones have been proposed as involved in the pathophysiology of EMS-related infertility, via altering both the eutopic and the ectopic endometrium. (1-3,6,7-9) However because not all women with reflux menstruation also have EMS, the retrograde menstruation theory cannot explain all case of EMS. One theory to complement the retrograde menstruation is the autoimmunity theory. EMS is associated with a chronic local inflammatory process and the presence of autoantibodies, and these are characteristics of other autoimmune diseases (AD). (10-12) If autoimmunity is present, immunomodulatory therapy for AD might then be used as a potential treatment for EMS without the shortcoming of current hormonal and surgical therapy. (13) In this review, we aim to connect the lines of evidence that link the (auto)immune dysfunction with the pathophysiology of EMS and the comparison and association with AD for developing potential treatments.

Pathophysiology of endometriosis

Animal models and human samples are paramount in the study of pathogenesis and progression of EMS. Many factors are involved in this disease, endocrine alterations but also an altered immune response against endometrial cells including inflammation and cytokine/chemokine expression. These last factors not only cannot effectively remove endometrial debris in the pelvic cavity from menstrual blood flow, but also can facilitate its implantation, neoangiogenesis and proliferation.

Endometrium

The ovarian steroid hormones regulate endometrial function and human menstruation. After human ovulation, the corpus luteum secretes high levels of progesterone to maintain endometrial receptivity should fertilization occur. In the absence of pregnancy the corpus luteum regresses, causing a sharp decline in circulating progesterone levels. This triggers a local inflammatory response in the endometrium involving infiltration of leukocytes, cytokine release, oedema and activation of matrix metalloproteinases. (14) The processes involved in endometrial repair appear to be analogous to classic wound healing and include inflammation, its resolution, angiogenesis, tissue formation and tissue remodelling. The human endometrium has two central balancing factors, estrogen and progestogen and these control autophagy in endometrial Ishikawa cells during the menstrual cycle. Ishikawa cells are typically cultured in the presence of both hormones, and an increased degree of autophagy and a higher incidence of apoptotic cell death is observed upon the withdrawal of one or both hormones. As a non-apoptotic form of programmed cell death, autophagy is the major cellular pathway for the degradation of long-lived proteins and cytoplasmic organelles in eukaryotic cells (15) and the induction of autophagy exerts a pro-apoptotic effect on normal human endometrial cells. (16) Based on accumulating evidences, the level of autophagy is most likely associated with the pathogenesis of EMS. The cross-talk between autophagy, a pathway that functions primarily in cell survival, and apoptosis, a pathway that invariably leads to cell death, is complex. The two pathways are regulated by common factors, they share common components, and each can regulate

and modify the activity of the other.(17,18) Many signals originally studied in the context of apoptosis activation induce autophagy, whereas signals that inhibit apoptosis also inhibit autophagy.(19) However, it does seem likely that the coordinated regulation of 'self-digestion' by autophagy and 'self-killing' by apoptosis may underlie diverse aspects of development, tissue homeostasis and disease pathogenesis. (18) Autophagy plays important roles in the process of cell growth, differentiation, tissue remodeling, cell immunity, environmental adaptation, and death such as apoptosis. EMS-derived endometrial tissues are characterized by reduced autophagy compared with the normal endometrium (20,21) and estrogen promotes the survival of human secretory phase endometrial stromal cells via CXCL12/CXCR4 up-regulation-mediated autophagy inhibition. (22) The ability of cells to undergo autophagy is reduced in the ectopic and eutopic endometrium of patients with EMS, and autophagy has been shown to be related to the pathogenesis and progression of EMS. In eutopic EMS foci, a slightly decreased level of autophagy is identified in both proliferative EECs and ESCs compared with the endometrium from controls. (20,21) Regarding ectopic endometriotic tissues, Ruiz et al. (23) have identified a decrease in autophagy levels in endometrial glandular epithelial cells (EECs) and endometrial stromal cells (ESCs) throughout the menstrual cycle; however, differences were observed among distinct endometriotic lesions (from ovaries, fallopian tubes, peritoneal, gastrointestinal, and skin). Furthermore the induction of autophagy in endometrial cells treated with estrogen alone (as in the proliferative phase) increase with the addition of progesterone (as in the secretory phase) and simultaneously diversification is observed with the removal of estrogen and progesterone (as in the menstrual phase). These findings demonstrate that the low level of autophagy observed in secretory phase ESCs is involved in the pathogenesis of EMS. (23) Accordingly, ESCs are primarily involved in the interaction between the endometrial tissue and the mesothelial cell lining of the peritoneum and play a fundamental role in the pathogenesis of EMS. Endometriotic cells inside the ovarian endometriotic cysts experience a persistent condition of oxidative stress with high levels of free redox-active iron that retrospectively act as an autophagic stimulus (24)

and on the other hand, a dramatic loss of the master inducer of apoptosis and negative regulator of cell proliferation, p53 (25) has been observed in ovarian endometriotic cyst tissues, which in addition to suggesting that apoptosis is impaired, may also be responsible for stimulating autophagy. According to a more recent study, the expression of HIF-1α (hypoxia-inducible factor-1α), a heterodimeric transcriptional factor mediating the cellular response to hypoxia, is increased in ovarian endometriotic lesions and enhances the migration and invasion of HESCs by upregulating autophagy in a hypoxic environment. Thus, autophagy is also induced through HIF-dependent pathways, which are involved in the high autophagy level detected in ovarian endometriotic lesions.(21)

EMS is an inflammatory disease: role of innate immune response

Monocytes/macrophages

The prime regulators of the innate immune response are macrophages which come into play in case of injury, damage and infection. Macrophages are an integral component of the mononuclear phagocyte system (MPS). After reaching peripheral tissues, they reside as macrophages or antigen-presenting cells (APC) including dendritic cells (DCs). In mouse models, in the absence of macrophages, endometriotic tissue retains the ability to adhere to the peritoneal layer. Peripheral monocytes and peritoneal macrophages have been studied extensively in pathogenesis of EMS. (26)

One of the main functions of macrophage is phagocytosis mediated by scavenger receptors for cell recognition and regulated by various cytokines and growth factors. The defect in phagocytic ability of macrophages in EMS has been associated with downregulation of scavenger receptors expression and reduced function of the CD36, a class B scavenger receptor. (27) Women affected of EMS have a significantly higher concentrations of PF macrophages, even when compared to cases with abdominal infections. In the latter condition, a predominance of neutrophils has been observed (85% of PF leukocytes). The mechanism responsible for such cell distribution is still unknown. Akoum et al. (28) demonstrated that peritoneal macrophages of these

women had an increased capacity to secrete MCP-1 (monocyte chemotactic protein-1) (28) a member of the small inducible gene family, which plays a role in the recruitment of monocytes to sites of injury and inflammation. When the macrophages were depleted by clodronate liposomes after the establishment of the endometriotic lesion, the glandular and stromal structure of the lesions was morphologically distorted and ultimately failed to grow. (26) This observation implies that macrophages are not only involved in the early immune escape of endometriotic cells, but also are favored later establishment and growth with the cytokines produced. Importantly, these findings showed that aberrant increased inflammatory cytokines produced by the endometriotic lesion and peritoneal immune cells, especially macrophages, would critically contribute to the pathogenesis of EMS in which they can interact with each other to convey a cascade of functions.

Cytokines.

The adaptive immune system includes of two main types of lymphocytes: T and B cells. Each of these originate from different lymphoid organs: the thymus and bone marrow, respectively. Cytokines are proteins produced and secreted by a variety of cells including stromal cells, fibroblasts, and endothelial cells. In the immune system they are produced by leukocytes and exert their function on other leukocytes or tissues that express the cytokine receptor . (29) Pro-inflammatory cytokine activated macrophages have an essential role in the onset and progression of EMS . Both the endometrial and infiltrating immune cells produce inflammatory cytokines, such as TNF-α, IL-1β, IL-4, IL-6, IL-8, IL-17 (10) that further stimulate a cascade of inflammatory response. (30) This creates a regulatory feed forward loop influencing both the progression and symptomatology of the disease (31) resulting in a unique microenvironment that contributes to these lesions being able to evade immune surveillance. (32) TNF-α mainly acts as a precursor to initiate inflammatory response at the acute phase by activating a cascade of other cytokines, such as IL-1, IL-6 and VEGF. (33) In addition it can promote the adherence of ectopic endometrial cells to the peritoneum (34) and

plays a crucial role on increasing the invasiveness of endometrial fragments by upregulating MMP and reducing the effect of tissue inhibitors of MMP. (35) IL-1 plays a central role in the regulation of inflammation and immune response and peritoneal IL-1β has been found to onset cascade of other cytokine production in endometriotic stromal cells, such as vascular endothelial growth factor (VEGF) to promote angiogenesis and (36,37) IL-6 stimulate stromal cell proliferation (38) sICAM-1 and is able to impair NK cell activity, (39,40) B cells proliferation and autoantibody production (41) IL-8 concentration in the peritoneal fluid and serum seems to be higher in women with EMS (42) than women without EMS. (43) In addition to macrophages, eutopic and ectopic endometrial cells are another important source of IL-8, (44) and also IL-17A released by endometriotic lesions significantly increase angiogenic cytokines (IL-8,VEGF,) and proinflammatory cytokines (IL-6 and IL-1β) in the peritoneal cavity favoring the establishment, proliferation and migration of endometriotic cells. (45,26)

T-cells

T-helper 1(Th1) T-helper 2 (Th2) imbalance has been associated with EMS wherein the pro-inflammatory Th1 profile dominates over the Th2 anti-inflammatory response. One of the key regulators of immune processes in EMS are regulatory T cells (Tregs) derived from CD4 lineage. Tregs are produced naturally in the thymus and express the forkhead box P3 transcription factor (Foxp3+). Cytokine-induced increase of Foxp3 expression drives Tregs differentiation/activation and suppresses the response of effector T cell proliferation and FoxP3-expressing CD4+ regulatory T cells (Tregs) play an indispensable role in the maintenance of self-tolerance and immune homeostasis (46) and are involved in various human diseases, such as autoimmune diseases, allergies, and cancer. (47-49) The absence or depletion of Tregs lead to multi-systemic autoimmunity in mice and humans. (50) Tregs induce immune tolerance by production of IL-10, TGF-β, and anti-inflammatory cytokines that inhibit T helper cell activation. In line with a role for a modified immunity in the pathogenesis of EMS, CD4+/FoxP3+ Tregs are present in endometriotic lesions. (51)

In humans, conflicting results have been obtained regarding whether populations of Tregs in the peritoneal fluid (PF) or peripheral blood (PB) differ significantly between patients with EMS and controls, (52-54) even if FoxP3 mRNA is increased in ectopic endothelial tissue, since the percentage of Tregs and its cytokines products is significantly reduced in the peripheral fluid from women with EMS compared to normal controls. However in the peritoneal fluid the Treg percentage is increased. (53) This discrepancy could suggest a differential immune modulatory system at the local and global levels. The polymorphisms of FOXP3 gene may change the quantity or function of Tregs as in AD, and FOXP3 gene was predominantly restricted to the function or cell numbers of Tregs. (55) A Brazilian study showed remarkable association on the FOXP3 polymorphisms associated with risk of idiopathic infertility and EMS. (56) Recently has been demonstrated that also TECK derived from endometrial stromal cells and macrophages promotes the differentiation and cytokines production of Tregs. (57) According to several studies, a strong association between Transforming growth factor-β (TGF-β) levels in PF and EMS has been observed, (58) and TGF-β induces FoxP3+ Tregs and inhibits the proliferation of immune cells and cytokine production via FoxP3-dependent and independent mechanisms. (59) Recently was assessed the immunotolerance of patients with EMS by analyzing Treg subpopulations in macrophages and monocytes derived from the PF and peripheral blood, respectively, of patients with EMS and controls. This study suggests that elevations in Tregs in patients with EMS are not systemic but are locally induced in the peritoneal cavity.(60)

Dendritic cells

Dendritic cells (DCs) are bone marrow-derived hemotopoietic cells which act as a "bridge" between innate and adaptive immunity. They are critically involved in the initiation and modulation of the adaptive immune response by recognizing and capturing antigens to naïve T cells as well as immune tolerance in inflammatory and neoplastic diseases. DCs are extremely heterogeneous and subpopulations can be defined based on their origin and function. Schulke et al. (61) demonstrated

significant increase of immature DCs (iDCs) in peritoneal endometriotic lesions and in the surrounding peritoneum when compared with paired eutopic endometrium and peritoneum distant from the lesion, (61) while the mature DCs (mDCs) have opposite results. This finding suggested that the endometriotic lesions or its peritoneal microenvironment would prominently recruit iDCs, rather than mDCs, to clear the ectopic endometrium. However, the increased iDCs may not be capable to present a detectable ectopic antigen in the endometriotic lesions for T cells to recognize due to its defectiveness in maturation. More recently, different subtypes of DCs were compared in peritoneal fluid from women with and without EMS. Myeloid conventional DC type 1 (MDC1s), type 2 (MDC2s) and plasmacytoid DC (pDC) were similar between groups, where MDC1s constituted the main proportion .(62) Further analysis of surface markers of MDC1s showed that Mannose Receptor (MR) + MDC1s were significantly increased in women with EMS. (62) The MR, a pattern recognition receptor belonging to the C-type lectin superfamily, mediates recognition and uptake of pathogens as well as endocytosis and phagocytosis. (63) It remains uncertain on why MR+MDC1s fail to clear the ectopic endometrial cells. The results of murine model to study the role of DCs of EMS is quite controversial. In a study conducted by Fainaru et al. (64) was reported that supplementation of DCs led to enhancement of endometriotic lesion growth and angiogenesis. (64,65) On the other hand, another study showed activated DCs within endometriotic lesions impaired the establishment of endometriotic lesions by enhancing the activity of T cells. (66) Although both study utilized the same process to ablate DCs, difference may relate to how the murine model was derived. The size and amount of endometrial biopsies being employed in the model are matter. Certainly, varying immune response may be resulted when compared suturing four pieces of 2-mm endometrial biopsy to peritoneal wall with injecting a large bulk of endometrial fragments into peritoneal cavity. Hence, similar comparable models are needed to elucidate the role of DCs in the development of EMS.

Natural killer cells (NK)

The peritoneal environment of women with EMS demonstrate quantitative and qualitative changes in monocyte/macrophage and natural killer cells (NK), multifunctional immune cells responsible for cell mediated immunity able to control the activity of other cells with a key role in the pathogenesis of EMS and the cytotoxic activity of peripheral and peritoneal NK cells was obviously decreased with the severity of the disease. (67-69) These changes may disturb the surveillance, recognition and destruction of misplaced endometrial cells and this situation may possible leads to EMS.(70) NK cells constitute a major component of the innate immune system and play a crucial role in anti-tumour immunity because of their innate ability to differentiate between malignant versus normal cells. (71) They participate in the host defense by firstly expressing different receptors binding to target cells, such as immunoglobulin G (IgG) while the second receptors would either promote cytotoxic activity, e.g. killer-activating receptors (KAR), or suppress cytotoxic activity, e.g. killer-inhibitory receptors (KIR). The decrease in NK-mediated cytotoxicity in the peritoneal fluid might promote retrograded endometrial cells to escape immune surveillance and promote its lesion establishment on the peritoneal cavity. Although the exact mechanism that brought upon aberrant NK cell cytotoxicity are not completely clear, previous literatures indicated the involvement in overexpression of KIR, such as KIR2DL1 (72,73) and increase of soluble ligands (MICA, MICB and ULBP-2) for the NKG2D receptor (a subclass of KAR) to impair NK cell function. (32) More recently, increased peritoneal IL-6 produced by ectopic endometrium was reported to display a suppressive effect on NK cell activity through the modulation of Src homology region 2-containing protein tyrosine phosphatase-2 (SHP-2) expression. (74) Similarly, higher level of IL-15 in peritoneal fluid and ectopic endometrium from patients with EMS has been demonstrated, when compared with control group, which enable endometrial stromal cells to escape immune surveillance by inhibiting cytotoxic activity of NK cells. (75) Consistently, platelet-derived transforming growth factor-β released by endometrial stromal cells suppresses the expression of NKG2D on NK cells leading to decreased cytotoxicity in women with EMS. (76,77) Again, the

aberrant cytokines in peritoneal fluid are the potential reasons causing dysfunction of NK cells in EMS. EMS showed higher percentage of cytotoxic CD16+ uNK cells and higher ratio of p46+NK:CD56+NK cells in the eutopic endometrium when compared with fertile control women. (78) This indicates that altered uNK cells in women with EMS may also generate an excessive inflammatory and hypoxia environment during embryo implantation or decidualization to increase the risk for infertility and miscarriage. (78)

Myeloid derived suppressor cells

Although the characteristics of aberrant cell mediated immunity in women with EMS has been identified since the last century, the underlying mechanisms remain unclear. Recently, we reported for the first time to the best of our knowledge that myeloid derived suppressor cells (MDSCs) play a critical role in the pathogenesis of EMS. (79) MDSCs are defined by their myeloid origin immature state (80) and fot their ability to potently suppress T cell responses as well as those of NK cells and B cells and are highly immunosuppressive. (81) These cells are found in small numbers in healthy status, and they rapidly expand in response to cancer, infections and inflammation. (82,83) In our study MDSCs were increased in peripheral blood of patients with EMS and MDSCs decreased following laparoscopic excision of the endometriotic lesions. This suggested that MDSCs might be involved in the process of EMS. Further analysis revealed that MDSCs promote the development of EMS in animal models. Based on the well-known immune suppressive role of MDCSs in tumors, we believe that MDSCs might contribute to the escape of ectopic endometrial cells from immune surveillance through 1) inducing differentiation of Tregs (84) 2) dysfunction of NK cells cytotoxic activity (85,86) and 3) promoting polarization of M2 macrophages which was characterized with decreased phagocytosis but increased tissue remodeling and angiogenesis (87,88) thereby contributing to the development of EMS.

Adhesion/invasion, angiogenesis and proliferation/growth

In order for endometriotic lesions to occur, the cells must invade and implant in

distant locations. Both monocyte chemotactic protein-1 (MCP-1) and regulated on activation, normal T cell expressed and secreted (RANTES) are significantly increased in peritoneal fluid from women with EMS and these concentrations are significantly correlated with severity of the disease. (89,90) The main source for the production of these two chemokines is from the ectopic endometrium. (91,92) In addition to being the chemotaxis of macrophages to peritoneal cavity, MCP-1 promotes the growth of endometriotic lesions by stimulating the proliferation and invasiveness of endometrial cells directly. (89,93) Also, there was evidence indicating that RANTES might be associated with the aberrant proliferation and apoptosis of endometriotic cells. (94) Cell adhesion molecules, including integrins, cadherins and ICAM-1, are expressed in endometrial and mesothelial cell surface to promote endometrial-mesothelial adhesion. Following adhesion, endometrial cells invade the peritoneal tissue by proteolytic digestion of extracellular matrix (ECM), such as serine proteases and matrix metalloproteinases (MMPs) (95) and have increased adhesive capacity to various components of the ECM including collagen type IV, laminin, vitronectin and fibronectin. ECM degradation could play a key role in initiation of EMS. (96) Furthermore growth and development of endometrial cells will heavily depend on neovascularization that is mediated by cytokines produced by immune cells, peritoneal cavity and retrograde sheds (summarized in figure 1). In particular the expression of VEGF, which is dependent on estradiol, hypoxia and peritoneal inflammatory cytokines, is known to be an important precursor toward promoting the pathological angiogenesis for the endometrial lesions to grow and develop.(97) With the neovascularization formed, the proliferation of endometriotic cells and endothelial cells are further stimulated by various growth factors circulated in the peritoneal fluid, such as insulin-like growth factor (IGF), TGF-β, platelet derived growth factor (PDGF), macrophage-colony stimulating factor (MCSF) and hepatocyte growth factor (HGF).(98,99) Glycodelin A (GdA), a protein secreted by endometrial glands during the secretory, but not the follicular phase of the menstrual cycle, is reduced in uterine flushings but also in the epithelial endometrium of women with EMS. These findings confirm that mRNA expression is reduced in these women and indicate that

proangiogenic factors have pivotal roles in the pathogenesis of EMS. (100,101)

Between innate immunity and humoral-mediated immunity

Complement system (CS)

One of the most important immune mechanisms taking part in the peritoneal clearance and inflammation is the complement system (CS). (102-104) The complement (C), a crucial component of the innate immune system, consists of over 30 small proteins which act as a cascade of proteases that activate each other in an enzymatic fashion, with effector mechanisms mediated by several specific cell receptors. The general function of the C is to recognize microbial pathogens and other target cells and let them lyse. The C cascade can be activated via one of three pathways: the classical pathway, the lectin pathway and the alternative pathway. These pathways are activated via different recognition molecules. We have demonstrated (105) that human follicular fluid (FF) contain functionally active C in amounts similar to those present in normal human serum. The presence of active C in FF may be very important for the function of the enzymatic multi-factorial mechanisms, included ovulation. (105) More recently has been demonstrated a higher concentration of C factors in peritoneal fluid of women with EMS in comparison to control.(106) Moreover, C levels were increased in women with an early stage of disease compared to advanced EMS. The results showed higher levels of C1q, the recognition molecule of the classical pathway that has the ability to modulate the functions of immune and non-immune cells and Mannose-Binding Lectin (MBL), a serum pattern recognition molecule, able to activate C in association with MASP proteases. Both the factors which started the classical and lectin activation of the C system, so it may suggest that the activation of C in women with EMS is correct and is a further link between EMS initiating events and immune surveillance via Complement system.

B-cells and autoantibodies

EMS shares many charateristics with AD, since women affected exhibit altered immune surveillance with abnormal functions of T and B cells, heightened humoral

immune response (high serum levels of IgG, IgA, IgM autoantibodies, and anti-endometrial antibodies) and inflammatory tissue damage.(11,107) The increased B-cell function was firstly documented in the 1980's. (108,109) Around the same year, Weed and coworkers (110) reported that C3 and IgG deposited in the endometrium of women with EMS is associated with a reduction in the serum total complement level, which suggested an intra-endometrial antigen-antibody reaction. (110) Further studies demonstrated higher incidence of autoantibodies in sera, cervical and vaginal secretions from women with EMS. (111-114) However, the correlation between autoantibodies concentration and the severity of EMS remains controversial. (115-118) As anti-endometrial antibodies are the most well-studied autoantibodies, it has been characterized as a potential diagnostic or follow-up marker on the assessment of treatment and recurrence toward EMS. Such profound anti-endometrial antibodies include transferrin and alpha 2 Heremans Schmidt (α2-HS) glycoprotein. The levels of endometrial transferrin in the peritoneal fluid of patients with EMS are significantly elevated, whereas the serum levels are lower when compared with controls. (111) With the concentration of transferrin and α2-HS glycoprotein being found higher in peritoneal fluid from women with EMS, it has been showed that transferrin attenuates FSH-induced differentiation of granulosa cells and might consequently lead to the varying degrees of ovarian dysfunction. (119) α 2-HS glycoprotein, a negative acute phase protein, suppresses the maturation conversion of mouse embryo zona pellucida protein ZP3 to ZP3f and causes polyspermia. (120) Furthermore the addition of antibodies specifically to transferrin and α 2-HS glycoprotein to sperm cells in vitro can inhibit motility and survival. (111) Finally, an alteration of cellular mediated immunity and higher prevalence of autoantibodies in women with endometriosis would consequently affect fecundity. This can lead to a disturbance on endometrial receptivity, oocyte quality, sperm motility, fertilization failure and embryotoxicity summarized in Figure 1.

On the other hand, the reason causing the elevated purge of autoantibodies in women with EMS is still uncertain. Case reports have suggested co-morbidity of EMS with the

autoimmune disorders alopecia universalis, autoimmune thyroiditis, multiple sclerosis (MS), and autoimmune progesterone dermatitis. (121,122) Recently identification of shared molecular signature indicate the susceptibility of EMS to MS, with shared genes up-regulating both EMS and MS such Neuronal growth regulator 1 (NEGR1), leptin receptor (LEPR), Cholinergic receptor muscarinic 3(CH3M3), Inositol 1,4,5-triphosphate receptor type 1 (ITPR1) the last able to disregulate oocyte meiosis and calcium signaling pathway. Different shared genes are able to down regulate both EMS and MS, such as Solute carrier family 8 member A1 (SLC8A1), Erb-b2 receptor tyrosine kinase 3 (ERBB3), Cadherin 1 (CDH1), Integrin subunit beta8 (ITGB8) Protein tyrosine phosphatase, non receptor type 11 (PTPN11), and Protein phosphatase 2 regulatory subunit B epsilon (PPP2R5E). The last one is able to disregulate oocyte meiosis. (123) A comparative evaluation of clinical and humoral immunologic abnormalities between SLE and EMS has observed that the diseases are associated, but that this association is confounded by hysterectomy, oophorectomy, and analgesic use. EMS was also associated with a lesser magnitude with RA risk, and this association was similarly influenced by hysterectomy, oophorectomy, and analgesic use. Perhaps the associations are primarily explained by a common influence of hormonal factors and immunologic abnormalities, although in these analyses little confounding was observed after adjustment for reproductive history and other hormonal factors. (124) Furthermore also Graves disease, an AD characterized by an IgG antibody binds to the thyroid-stimulating hormone receptor (TSHR) is linked with EMS. (125) This association was explained for the high incidence of positive antinuclear antibodies (ANA) in both the disease and for differential expression of the estrogen receptor beta gene (ESR2) confirmed in patients with EMS and associated with susceptibility to Graves disease.(126,127)

Another possible explanation that can lead to self-tolerance breakdown women with EMS (128) is the overexpression of B lymphocyte activating factor (BAFF), alternatively called B lymphocyte stimulator (BLyS), member of the tumor necrosis factor (TNF) ligand superfamily. Increasing evidence suggests that BAFF is essentially implicated in the pathogenesis of B cell-mediated AD and increased serum

levels of BAFF were reported in both non-organ-specific AD (such as systemic lupus erythematosus and Sjögrens's syndrome) and organ-specific conditions. (129-131) In addition, as the mRNA levels expressed by macrophages and its receptor BCMA expressed by plasma cells was strongly up-regulated in endometriotic lesions, this indicated their role in facilitating the survival of plasma cells. (128)

Other studies showed that significantly elevated IgG antilaminin-1 antibodies are strongly associated with EMS in infertile patients. (132) Laminin is a major multifunctional basement membrane glycoprotein with at least 15 known isoforms. It plays a critical role during embryo implantation by synthesizing network-forming complement during early embryo development. Also, it has been found to elevate the trophoblast adhesion to the maternal extracellular matrix and then decidua in endometrium, which further promote proliferation and differentiation of trophoblast when interacts with integrin receptors. In a study conducted by Inagaki and coworkers, they found significant association between IgG anti-laminin-1 antibodies and infertile patients with endometriosis for stage II or more. (132) The same group also demonstrated that anti-laminin-1 antibodies are significantly higher in women with recurrent miscarriage when compared with healthy controls, which causes a disruption in early reproductive stages by interfering with embryogenesis and placental development. (133,134) Moreover anti-laminin-1 in follicular fluid was noted to be related with oocyte maturation, it affected oocyte quality resulting in reduced fertility. (135,132) It was demonstrated that these antibodies may directly interfere with the function of laminin-1 to disrupt early reproductive stages and be involved in the development of EMS. In light of these findings, anti-laminin-1 antibodies might be clinically important in development of autoimmune-mediated reproductive failure and the antibody assessment may provide a novel non-invasive diagnosis of EMS. (136)

Role of autoimmune-related genetics in endometriosis

There is accumulating evidence to support the etiology of EMS as an epigenetic disease, even if remains to be studied the role of epigenetic factors in the development

of EMS. DNA methylation (hypo or hypermethylation) plays an important role in cellular processes and regulation of gene expression and a number of aberrantly expressed genes reported in EMS, such as aromatase (key molecule for estrogen production), E.cadherin, Steroidogenic factor-1 (SF-1) and others are related to aberrant DNA methylation. (137,138) Common genetic polymorphisms related in immune system were both detected in EMS and AD, including region in the genes of FOXP3, FCRL3, NF-κB and B lymphocyte stimulator. (139) Fc receptor-like 3 (FCRL3) gene encodes a glycoprotein belonging to the immunoglobulin receptor superfamily. It plays a role in B cells differentiation into autoreactive cells through the modulation of signal transduction via activation/inactivation of signaling tyrosine protein kinases. (140) As reported by Bianco et al., (141) FCRL3-169C/T was significantly associated with risk of endometriosis regardless of the stage of the disease. (141) Also, the FCRL3-169C allele was found to be correlated with an increased production of autoantibodies. (142) NF-κB, a major transcription factor of immune response leading to cell apoptosis and growth. It was reported to play an important role to mediate anti-apoptosis, growth of endometriotic cells, invasion, angiogenesis and cytokine production in EMS (143) and recently, a common insertion/deletion polymorphism (-94 insertion/deletion ATTG) in the NF-κB gene was identified in SLE. (144)

The depletion of ATTG results in the loss of binding to nuclear proteins and reduces promoter activity. In EMS the frequency of the ATTG (2)/ATTG (2) genotype and ATTG (2) allele was significantly increased when compared with healthy individuals. This suggested that the polymorphism of NF-κB gene might be a predisposition gene toward EMS susceptibility.(145)

AD are usually associated with certain HLA alleles.(146) Similar phenomenon has also been observed in EMS. (11)

In the Japanese population, Class I HLA-B54 and HLA-Cw7, class II HLA-DRB1*1403 and HLADQB1*0301 were associated with EMS.(147-148) Another study found that EMS was associated with class I HLA-B*0702 alleles, in linkage disequilibrium with HLA-A24, HLA-Cw*0702 and class II

HLA-DRB1*0101 alleles (149) while in the Chinese population, class I HLA-B46, class II HLA-DRB1*15, and HLADQA1*0401 were reported to be associated with EMS (150-152). However, this was not replicable in the Korean population. (153) Similarly, the association between HLA alleles and EMS was not consistent in Europe. In a study conducted by Sundqvist et al., they found significant association between CCL21, HLA-DRB1 and EMS in the Swedish/Belgian population (154) however this association was not found in the Polish population. (155) The disparity between the different populations indicated multiple genetic factors might be involved to result in variable prevalence of EMS among different ethnicities.

Impact of immunological dysfunction on endometriosis associated infertility

The pathophysiology of EMS involves chronic dysregulation of inflammatory and vascular signaling.

Galectin-1 and -3 are overexpressed in various forms of endometriotic tissues. Galectins belong to a subfamily of lectins and regulate a wide variety of key biological processes, such as cell growth, proliferation and differentiation, apoptosis, but are also pivotal in immune responses since they regulate host-pathogen interactions, acute and chronic inflammation, and immune tolerance. (111, 156-160) Higher galectin-3 concentrations are also detected in peritoneal fluid samples from women with EMS than from controls(161,162) and galectin-1 is strongly expressed by human uterine natural killer (uNK) cells compared to peripheral blood NK cells (pNK). These CD56+galectin-1+uNK cells comprise ~70% of maternal leukocytes at the implantation site, promote angiogenesis and trophoblast invasion. (163, 164)

Along the way, other autoantibodies have also been found in infertile women with EMS undergoing assisted reproduction. A retrospective study tested the effect of circulating IgG, IgM and IgA isotype antibodies to cardiolipin, phosphatidylserine (PS), phosphatidylethanolamine (PE), phosphatidylglycerol (PG), phosphatidylinositol (PI), phosphatic acid (PA), histone 2A (H2A) and 2B (H2B) fractions, single-stranded DNA (ssDNA) and double-stranded DNA (dsDNA) in women with and without endometriosis on IVF outcome. (165) The result showed

three or more positive autoantibodies were detected in 50% of patients with EMS and the pregnancy rates in autoantibody-positive group and autoantibody-negative group was 23% and 46%, respectively. (165) Importantly, administration of corticosteroid for patients with autoantibodies improved the pregnancy rate. (165) A similar study analyzed the presence of several different antinuclear antibodies (ANA), antiphospholipid antibodies (APA), antithyroid antibodies (ATA) and lupus anticoagulant in infertile women with recurrent pregnancy loss. (166) The result showed that positive rate of autoantibodies was similar in women with reproductive failure and EMS, which is higher than fertile controls. (166) Based on these evidences, autoantibodies could be a potential monitoring marker in infertility and recurrent miscarriage associated with EMS.

Current therapies for EMS

Despite a range of symptoms, diagnosis of EMS is often delayed due to lack of non invasive, definitive and consistent biomarkers and until now the visual inspection of the pelvis at laparoscopy with histologic confirmation is the gold standard for diagnosis of EMS. (167,168) Furthermore all currently available treatments of EMS are suppressive, not curative. They are associated with the temporary relief of symptoms during treatment. On treatment discontinuation, recurrence of the symptoms is the rule. For instance, EMS-associated pain can continue after medical treatment or conservative surgery. The current treatment options for EMS-associated pain are contraceptive rather than fertility-promoter therapy. Women desirous of pregnancy who have painful EMS, nonsteroidal anti-inflammatory drugs (NSAIDs) appear to be the only medical option consistent with the maintenance of fertility with a pretreatment with a gonadotropin-releasing hormone (GnRH).

Hormonal Therapies

GnRH agonists are usually the first-line agents because they are highly effective at suppressing ovarian hormone production and able to inhibit the growth of the

extrapelvic endometrial tissue. Failure of medical treatment is frequently encountered with these aggressive disease phenotypes. (169) Selective progesterone receptor modulators (SPRM) can have variable effects on progesterone receptors from different tissues, ranging from being a pure agonist or a mixed agonist/ antagonist to a pure antagonist. Mifepristone (RU486) was shown to have a positive effect on pain symptoms. (170,171) Ulipristal acetate and asoprisnil are other members of the same family but feasibility of ulipristal acetate and others SPRM for the treatment of EMS has yet to be determined. Raloxifene, a commercially available selective estrogen receptor modulator (SERM), has been used for the treatment of postmenopausal osteoporosis. Raloxifene was tested at various doses in a rat model of EMS and was shown to have an estrogen-antagonist effect in rat uterine tissue (172) but the effectiveness on EMS in humans has yet to be evaluated. Aromatase inhibitors are a treatment option that usually is reserved for managing severe, intractable EMS-associated pain in combination therapy with oral contraceptive pills, progestins, and GnRH analogues and patients should be counseled about the off-label nature of its use for endometriosis-associated pain. (173) Nevertheless these treatment remains suboptimal owing to the side effects, e.g. hypoestrogenic condition, and unsatisfactory outcomes to restore fertility.

Non hormonal Treatments : Immunomodulatory therapies

Many studies have evaluated the diagnostic value of biomarkers of EMS, but no data on recommended biomarkers in endometrial tissue, menstrual or uterine fluids and immunologic markers in blood or urine for clinical use as a diagnostic test for EMS. Recently Vodolazkaia A et al, (174) selected a diagnostic panel of four biomarkers (annexin V, VEGF, CA-125 and sICAM-1/glycodelin) in plasma samples obtained during menstruation. A multivariate analysis could predict US-negative endometriosis with a sensitivity of 81– 90% and a specificity of 63 – 81%. (174) The relevance of this selected diagnostic panel (annexin V, VEGF, CA-125 and sICAM-1/glycodelin) is confirmed by the fact that these biomarkers are involved in apoptosis, angiogenesis,

adhesion and tumorogenesis, which are highly related to the pathogenesis of EMS. (174,175) However, although EMS remains largely benign, malignant transformation may occur in up to 1% of cases, most commonly from ovarian lesions, (176) and this transformation could be due to a culmination of a multifaceted complex of pathogenic factors in conjunction with endocrine imbalance and oxidative stress and immune surveillance dysregulation.(177) In women with EMS most of the studies have focused on secreted chemokine profile (178) or immune cells resident in the peritoneal fluid (macrophages and NK cells) and/ or isolated from peripheral blood (T lymphocytes, NK cells). (179-180) and the women affected show dysfunctional, increased accumulation of regulatory T suppressor cells all factors able to favor chronic inflammation and promote initiation and progression of EMS associated ovarian cancer. Etanercept, a TNF-α blocker, a potential immunomodulatory agents was used in a baboon model, and led to a statistically significant decrease in red lesion surface area in the treatment group with a trend toward a decrease in the absolute number of red lesions. (181) Another immunomodulator (loxoribine) caused a reduction in NK cells and endometriotic lesions in a rat model (182) and a similar reduction of endometriotic lesions was observed with lipoxin, (183,184) rapamycin, (185) and pentoxifylline.(186) A Cochrane review (187) evaluated four clinical trials, and demonstrated a lack of evidence to recommend pentoxifylline for pain relief or to improve the chances of spontaneous pregnancies. So, even if these novel therapeutic agents appear promising on the treatment of EMS, further studies from multi-center clinical trials are still needed prior to be recommended as a routine regime for women with EMS. (187) In the last few decades, numerous studies have investigated the link between vitamin D (VD) ($1,25(OH)_2D_{3)}$ and the incidence and severity of AD. (188) VD is is a steroid hormone that, in addition to its actions on calcium and bone metabolism, exhibits a plethora of regulatory effects on immune cells. (189) Active VD can work as a positive immunomodulator on both the innate and adaptive immune responses (190) and hypovitaminosis D is highly prevalent in autoimmune diseases and correlate with disease activity and comorbidities. (190) VD exerts a broad range of biological activities since "…a lack of vitamin D renders patients liable to the

development of an autoimmune disease." (190) In recent years, accumulating evidences showed that VD supplementation could be used as an immunomodulator for managing also EMS, since EMS shares some characteristics with AD, (11) and inflammatory changes in the peritoneal cavity may be associated with lesion development. Furthermore other comorbid AD (i.e., systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis) (123,124) can coincide with the presence of EMS.(191,192) Mariani et al. (193) and other groups (194) have demonstrated that rodents supplemented with $1,25(OH)_2D_3$ showed a regression of endometriotic lesion by significantly reducing VEGF and MMP-9, and increasing MMP-2 inhibitors. (195) Therefore VD might be a novel therapeutic approach for managing EMS as an AD through its immunomodulatory and anti-inflammatory properties. Importantly, dairy products rich in calcium and VD have been linked to lower the risk of developing EMS in humans. (196)

Hydroxychloroquine (HCQ), derivative of Chloroquine, firstly used to treat malaria, is an effective therapeutic agent for a range of autoimmune disorders non-organ specific, such as SLE, rheumatoid arthritis, and mixed connective tissue disorders.(197) HCQ can antagonize communication among cells in the immune system that are inappropriately activated, and recently Ruiz et al. (23) identified HCQ as a potential new non-hormonal treatment demonstrating the therapeutic effects on human endometriotic cells in an established mouse model of EMS.

Also a wide variety of antiangiogenic agents has been evaluated in vitro as potential treatments for EMS. These include growth factor inhibitors, endogenous angiogenesis inhibitors, fumagillin analogues, statins, cyclooxygenase-2 inhibitors, phytochemical compounds, immunomodulators, dopamine agonists, peroxisome proliferator-activated receptor agonists, progestins, danazol, and gonadotropin-releasing hormone (GnRH) agonists. However, clinical evidence for the efficacy and safety of most of them is still lacking. (198,199)

Recent data have linked disorders of the C system activation and pathogenesis of EMS.(200) Under normal circumstances, C activation is tightly controlled by several

regulatory proteins to minimize host tissue damage. In the available literature, there is no information about the role of C1q and C1INH in the formation and development of EMS. C1INH has been shown to inhibit the C safely and an impairment in the activity and concentration of C1INH can cause such diseases as hereditary angioedema (HANE), defined as a local, noninflammatory, self-limiting edema or the systemic lupus erythematosus (SLE). (201) One of the mainstays in long term management of HANE is long-term therapy with danazol, a mild androgen capable of correcting low Cl INH concentrations and of almost completely putting into remission the typical symptoms of the disease, (202) and is capable to improve ovarian condition in HANE. (203) Another important hormonal therapy for EMS, GnRH agonists, can modulate serum C function *in vivo* (204) and GnRH agonists were used also in long term prophylaxis of HANE attacks. (205) Furthermore C pathway was demonstrated associated with all gene expression changes (benign EMS, atypical EMS and EMS associated ovarian cancer) (104) so these findings reveal that chronic inflammation in EMS is dominated by C system activation and suggest a link between initiating events and immune surveillance via C. New therapies could point also to this pathway as a potential target for early prevention of EMS.

Conclusions

EMS, still incurable and common disease, that impacts the quality of life, represents a unique immunological scenario. The aberrant changes in cellular immune response and its cytokines are found to be related to the pathophysiology (immune escape, adhesion, invasion, angiogenesis and proliferation). Also, the presence of autoantibodies is another consequence of dysfunction of immune system. These immunological alterations cause decreased fecundity or even infertility by affecting endometrial receptivity, follicular fluid, sperm mobility and embryo cytotoxicity.

Although EMS is still not defined specifically as an AD, both diseases share several similar characteristics, such as female (and hormonal) predominance, genetic polymorphisms, immunological abnormalities and chronic condition. Diagnostic delays are common and may lead to a decline in reproductive potential and fertility,

therefore more research is needed in this area of medicine.

Recently potential biomarkers including cytokines and autoantibodies are developing promisingly for use in early screening, to reduce late diagnosis and the cost of surgical intervention, but also new therapeutic strategies able to provide long-term benefit and ameliorate fertility in these women.

Figure 1. Schematic representation of the complex pathophysiology of endometriosis with immunity. Endometrium flow through fallopian tube into peritoneal cavity during menstruation. (A) Retrograded endometrium can usually be cleared by peritoneal immune cells in normal healthy individuals. (B) However, once an endometriotic fragment bypassed the immunosurveillance and adhere onto the peritoneum wall, a cascade of cytokines regulation will begin. Impaired NK cell activity with lower expression of KAR but higher expression of KIR, decreased phagocytosis of macrophages with decreased expression of scavenger receptors, and induction of Tregs are involved in helping endometrium escaping from peritoneal immunosurveillance. Dramatic increase of MDSCs within short time after the presence of endometrium in peritoneal cavity might be the reason causing depressed immunosurveillance. Cytokines ICAM-1, IL-6, IL-8, VEGF etc. released by ectopic endometrium and immune cells might be another reason causing immune tolerance and they also contribute to following adhesion, invasion, angiogenesis and growth. Higher frequency of autoantibodies in peritoneal cavity is also identified in women with endometriosis. (C) The changes of cellular and hormonal immune response in peritoneal cavity, follicular fluid and endometrium lead to decreased fecundity, even infertility by reducing endometrial receptivity, oocyte quality, sperm mobility and embryo cytotoxicity. KAR= killer-activating receptors; KIR= killer-inhibotory receptors; mDC=mature dendritic cells; iDC=immature dendritic cells; Tregs=T regulatory cells; IL= interleukin; PDGF=; ICAM-1= intercellular adhesion molecule-1; MCP-1= monocyte chemotactic protein-1; TGF-β =transforming growth factor-β ; VEGF= vascular endothelial growth factor; TNF-α = tumor necrosis factor-α.

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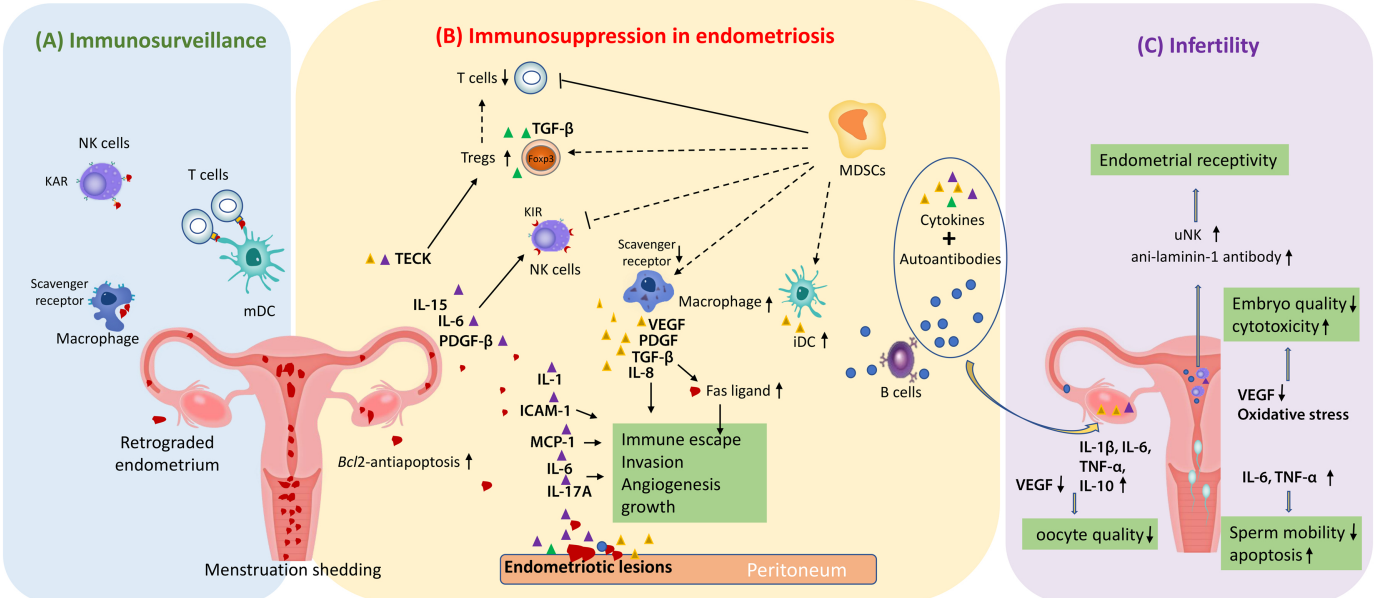
(A) Immunosurveillance
NK cells
KAR
T cells
mDC
Scavenger receptor
Macrophage
Retrograded endometrium
Menstruation shedding
(B) Immunosuppression in endometriosis
T cells
TGF-β
Tregs
Foxp3
MDSCs
KIR
NK cells
TECK
Scavenger receptor
Macrophage
iDC
IL-15
IL-6
PDGF-β
VEGF
PDGF
TGF-β
IL-8
Fas ligand
IL-1
ICAM-1
MCP-1
IL-6
IL-17A
Bcl2-antiapoptosis
Immune escape
Invasion
Angiogenesis
growth
Endometriotic lesions
Peritoneum
Cytokines
+
Autoantibodies
B cells
(C) Infertility
Endometrial receptivity
uNK
ani-laminin-1 antibody
Embryo quality
cytotoxicity
VEGF
Oxidative stress
IL-1β, IL-6,
TNF-α,
IL-10
VEGF
oocyte quality
IL-6, TNF-α
Sperm mobility
apoptosis

Figure 1