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Uterine Leukocyte Function and Dysfunction: A Hypothesis on the Impact of Endometriosis

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Abstract

Endometriosis is a chronic inflammatory disease characterized by the growth of endometrial glands and stroma outside of the uterus. The disease affects approximately 10–15% of women of reproductive age and presents with clinical symptoms of pelvic pain and infertility. Changes in the leukocyte populations within the ectopic tissue and eutopic endometrium have been reported, and data suggest these alterations contribute to the pathology and symptoms of the disease. In this review, we discussed differences when comparing uterine NK cells and regulatory T cells within the eutopic endometrium between patients with endometriosis and healthy patients, and how these differences relate to implantation failure and/or decreased clearance of menstrual tissue in patients with the disease. The data demonstrate a critical need to examine endometrium and menstrual tissue in patients with endometriosis excluded from studies examining unknown causes of infertility and heavy menstrual bleeding. The information gathered from excluded patients will further enhance our understanding of how the immune system contributes to the pathophysiology of endometriosis and help to identify biomarkers for patients at higher risk for developing endometriosis-associated infertility.

Keywords

Endometriosis; implantation failure; menstruation; NK cells; regulatory T cells

Introduction

Endometriosis is a chronic inflammatory disease characterized by the growth of endometrial glands and stroma outside of the uterus.[1] The disease affects approximately 10–15% of women of reproductive age,[2] and the pathogenesis is due to multiple factors that vary among patients.[3] The primary clinical symptoms of endometriosis are infertility,[4–7] poor oocyte development,[8] dysmorphology of the Fallopian tubes, and intense abdominal pain from ectopic lesion growth.[9,10] Sampson's theory of retrograde menstruation is currently the most widely accepted theory for the initiation of endometriosis.[11] However, additional

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mechanisms have also been proposed to explain endometriotic lesions in locations other than the peritoneal cavity such as coelomic metaplasia and metastasis of endometrial cells through the lymphatic system.[12,13] Sampson's theory of retrograde menstruation is supported by animal models,[14] including the baboon model that we have used extensively in our laboratory.[15] Ectopic lesions, with similar histology to those reported in human cases, develop in the animals following inoculation of menstrual tissue into the peritoneal cavity.

Leukocytes within the ectopic tissues in patients with endometriosis contribute to the survival and growth of the lesions. Studies examining ectopic endometrium have reported presence of regulatory T cells[16,17] and M2 macrophages,[18] low phagocytic activity of macrophages,[19] high ratios of Th2:Th1 cells,[20] and absence of NK cells[21] in the lesions. This combination of leukocytes contributes to a 'pro-growth' and 'pro-survival' environment, rather than destruction, for ectopic endometrial tissue. In addition, the leukocyte populations within the ectopic tissues of patients with endometriosis may induce changes in the leukocyte populations of the eutopic endometrium. The leukocytes within the eutopic endometrium contribute to the stromal microenvironment of the uterus through multiple mechanisms, as reviewed below. Thus, endometriosis-induced changes in the eutopic endometrial leukocyte populations may directly affect the ability of the uterus to function.

The main function of the uterus is to provide an environment for implantation and growth of the developing embryo and the fetus. Each month, under the control of ovarian hormones, the stratum functionalis of the endometrium proliferates and the endometrium then differentiates in response to luteal phase progesterone in preparation for implantation. If implantation does not occur, the endometrium must be shed and the shed fragments must be eliminated to allow for the cycle to continue. Both of these stages in the monthly life cycle of the uterus, rebuilding the endometrium and shedding and eliminating the stratum functionalis in the absence of implantation, involve orchestration of endometrial leukocytes. When the endometrial leukocyte populations are dysregulated in number and/or function, the ability of the uterus to correctly regenerate the endometrium and/or eliminate shed endometrial cells is likely to be dysregulated as well. This review will focus on differences regarding the leukocytes populations within the eutopic endometrium of patients with endometriosis compared to patients without endometriosis. We will also discuss how these differences relate to implantation failure and/or decreased clearance of menstrual tissue in patients with the disease.

Differences in uterine NK cells associated with implantation failure

Uterine natural killer (uNK) cells are the predominant leukocyte population in the normal human endometrium.[22] The level of NK cells varies during the menstrual cycle, representing 40% of the total leukocyte population during the proliferative phase, and increasing to 60% by mid-secretory phase.[23] Approximately 70–80% of uNK cells are characterized as $CD56^{bright}CD16^{-}$.[24] Activated uNK cells can produce angiogenic factors (VEGF, ANG2) that promote spiral artery remodeling and secrete cytokines (GM-CSF, CSF-1, TNFα, INFγ, TGFβ, LIF, IL2, CXCL10, CXL12) which direct the migration and invasion of the trophoblast.[25–27] The activity of uNK cells is controlled by activating receptors, including

the natural cytotoxicity receptors (NKp30 and NKp46),[28] as well as inhibitory receptors, including the killer immunoglobulin-like receptor (KIR) and immunoglobulin-like transcript-2 (ILT2)[26]. In addition, the expression of CD16 on uNK cells coincides with increased cytotoxic activity.[29]

Dysregulation of uNK number and/or function could lead to implantation failure in patients with endometriosis, as reviewed by Thiruchelvam et al.[30] In studies examining patients without endometriosis, a higher concentration of CD56+ uNK cells was reported in women with unexplained recurrent pregnancy loss compared to fertile women.[31–34] However, other studies have reported no difference between the patients suffering from recurrent pregnancy loss and fertile patients[35–38] Likewise, the data from studies examining uNK cells in patients with endometriosis are also variable. Some laboratories have reported a lower percentage of $CD56^+$ NK cells and a defect in NK activity in the eutopic endometrium of women with endometriosis.[39–41] Studies from our laboratory did not observe a difference in the percentage of CD56+ uNK cells when comparing patients with endometriosis to healthy controls. However, we did report a higher percentage of CD16+ cells (associated with cytotoxicity) and NKp46+ NK cells in the endometrium of patients with endometriosis who were infertile or experienced recurrent pregnancy loss, compared to fertile patients with endometriosis.[42] These data suggest that increased activity of uNK cells, as controlled by specific receptors, may contribute to a stromal microenvironment that is less receptive to embryo implantation. In support of this hypothesis, a recent report by Nowak et al.[43] demonstrated a significant risk for endometriosis associated with the presence of specific KIR receptors and their MHC I ligands (KIR2DS4del and HLA-C C2) and a lower risk of endometriosis in patients with different KIR receptors (KIR2DS5). Thus, additional studies are needed to elucidate the differences between uNK cells in patients with endometriosis versus patients without endometriosis and determine which changes increase the risk of implantation failure in these patients.

Differences in uterine NK cells associated with reduced clearance and/or increased viability of shed endometrial tissue

In the absence of implantation, $granzyme^+$ $perforin^+$ NK cells disperse throughout the stratum functionalis during the secretory phase.[44] Recruitment of $granzyme\ B^+$ $perforin^+$ NK cells to secretory endometrium coincides with apoptosis of glandular epithelium.[45] Perforin and granzymes are released from the granules in NK cells undergoing exocytosis. Perforin is a protein that polymerizes to form pores in the membranes of cells targeted by NK cells, allowing granzymes to enter into the cytosol of the target cells. Granzymes then initiate apoptosis of the target cells, such as the glandular epithelial cells, by activating caspases.[46] As menstruation ensues, the uNK cells also undergo apoptosis.[47] Decreased perforin and granzyme expression by uNK cells and/or decreased apoptosis of NK cells could lead to increased survival of endometrial fragments during menstruation. This, in turn, may increase the amount of tissue entering the peritoneal cavity following retrograde menstruation. Studies by Berbic et al.[48] reported changes in uNK cells in patients with heavy menstrual bleeding, and a recent study by Biswas Shivhare et al.[49] specifically reported a reduction of uNK cells in the late secretory phase of patients with heavy

menstrual bleeding. Unfortunately, although heavy menstrual bleeding is a symptom in many patients with endometriosis, patients with endometriosis were excluded from these studies. Future studies measuring uNK cell numbers and granzyme/perforin levels at the onset of menstruation are needed to determine whether changes in the uNK cell populations that coincide with menstruation are dysregulated in patients with endometriosis.

Differences in uterine regulatory T cells associated with implantation failure

T cells are a diverse population of lymphocytes identified by absence/presence of specific CD markers, transcription factors, cytokine production, and cytotoxic capacity.[50] Like uNK cells, the levels of uterine T cells (CD3+) vary throughout the menstrual cycle, representing 50% of the leukocyte population during the proliferative phase, and decreasing to <10% of the leukocytes population by the late secretory phase.[51] In contrast to $CD3^+$ T cells in peripheral blood, uterine $CD3^+$ T cells consist of a larger proportion of $CD8^+$ cells (66%) and smaller proportion of $CD4^+$ cells (33%).[51] The $CD4^+$ T cell population includes Th1, Th2, regulatory T cells (Tregs), and Th17 cells, each of which secretes specific cytokines with wide-ranging effects.[52] Tregs, often identified by expression of the transcription factor forkhead box P3 (FoxP3), secrete immunosuppressive cytokines that promote a state of immune tolerance.[53] Data suggest that the immune tolerance created by Tregs is required for successful embryo implantation, as reduced levels of Foxp3 mRNA have been reported in patients with primary infertility compared to fertile patients.[54] These findings lead our laboratory to examine Tregs in the baboon model of endometriosis. A decrease was observed in $FoxP3^+$ cells and FoxP3 mRNA in the endometrium following induction of endometriosis in baboons.[17] In contrast, the $FoxP3^+$ cells and FoxP3 mRNA are maximum in the ectopic endometrium, similar to studies by Basta et al.[55] that reported higher levels of $FoxP3^+$ cells in ectopic endometrium compared to eutopic endometrium from healthy patients. Although these findings contradict the increased levels of $FoxP3^+$ cells and FoxP3 mRNA reported in endometrium of women with endometriosis,[16,56] the data from the baboon model and human patients suggest that endometriosis alters the level of Tregs within the endometrium. Additional studies are therefore needed to assess the number and function of uterine Tregs in more patients with endometriosis, particularly in those patients with endometriosis who are infertile. Likewise, the Treg:Th17 ratio within the endometrium of patients with endometriosis needs to be assessed and compared to the ratios recently reported in studies examining these ratios in endometrium from healthy patients.[20] Disruptions in Treg/Th17 ratios have been associated with recurrent pregnancy loss and pre-eclampsia[57] and thus may also play a role in endometriosis-associated infertility. More information regarding changes in uterine Tregs will assist in identifying targets for future endometriosis therapy.

Differences in uterine regulatory T cells associated with reduced clearance and/or increased viability of shed endometrial tissue

Minimal information currently exists regarding the role of Tregs in menstruation and the viability of shed endometrial tissue. As proposed by Berbic et al.,[58] macrophages, mast cells, dendritic cells, neutrophils, and eosinophils all play a role in menstruation and their

functions are affected by regulatory T cells. If the functions of uterine regulatory T cells are altered by endometriosis, this may promote increased survival of shed endometrial fragments, contributing to the progression of the disease. Additional studies examining uterine Treg activity and leukocytes in the menstrual tissue from patients with endometriosis are needed to test this hypothesis.

Concluding statement

Endometriosis is a complex, systemic disease. The two models presented in Fig. 1 demonstrate how the ‘pro-growth/pro-survival,’ indicated as ‘regulatory’ leukocyte populations, may arise in the ectopic lesions. As shown in the endogenous model, it is possible that some patients may inherit factors that promote development of more ‘regulatory’ leukocytes within their eutopic endometrium. Following retrograde menstruation, these ‘regulatory’ leukocytes promote the survival of the lesions once the eutopic endometrial tissue enters the peritoneal cavity. On the other hand, as shown in the exogenous model, it is possible that other patients may have ‘non-regulatory’ leukocytes in the ectopic endometrium. However, following retrograde menstruation, these leukocytes may respond to factors in the peritoneal microenvironment and differentiate into a ‘regulatory’ phenotype. Both pathophysiologies are possible and are difficult to dissect in human patients, as the average delay in diagnosis of endometriosis is 8–10 years from the onset of the disease.[59] In either case, the cells within the ectopic lesions survive, differentiate, and invade the serosa, resulting in the activation of an inflammatory response. The models in Fig. 1 also portray how the ectopic lesions, developed through either the ‘endogenous’ or ‘exogenous’ mechanism, may eventually affect the leukocyte populations in the eutopic endometrium. This could easily occur when cells and/or secreted factors derived from the ectopic sites circulate through the mesenteric lymphatic drainage and systemic blood that eventually recirculates through uterine blood vessels.

To further enhance our understanding of the relationship between the ectopic and eutopic endometrium, results comparing the ratios of leukocytes within the ectopic endometrium, peritoneal cavity, peripheral blood, eutopic endometrium, and menstrual tissue are needed. Determining the ratios of leukocytes between these tissues within individual patients may provide an internal control for comparisons. Likewise, it is possible that comparing ratios between patients may reduce the variability in the data reported among different studies. In addition, samples from patients with endometriosis are often excluded from studies involving patients with unexplained recurrent pregnancy loss, infertility, or heavy menstrual bleeding. However, the data reviewed above demonstrate a critical need to examine the tissue in these excluded patients to understand the infertility associated with endometriosis. The information gathered from excluded group of patients will further enhance our understanding of how the immune system contributes to the pathophysiology of endometriosis and help to identify biomarkers for patients at higher risk for developing endometriosis-associated infertility. Finally, the changes in the eutopic endometrium that relate to implantation defects and/or ineffective clearance of menstrual tissue may serve as targets for future treatments.

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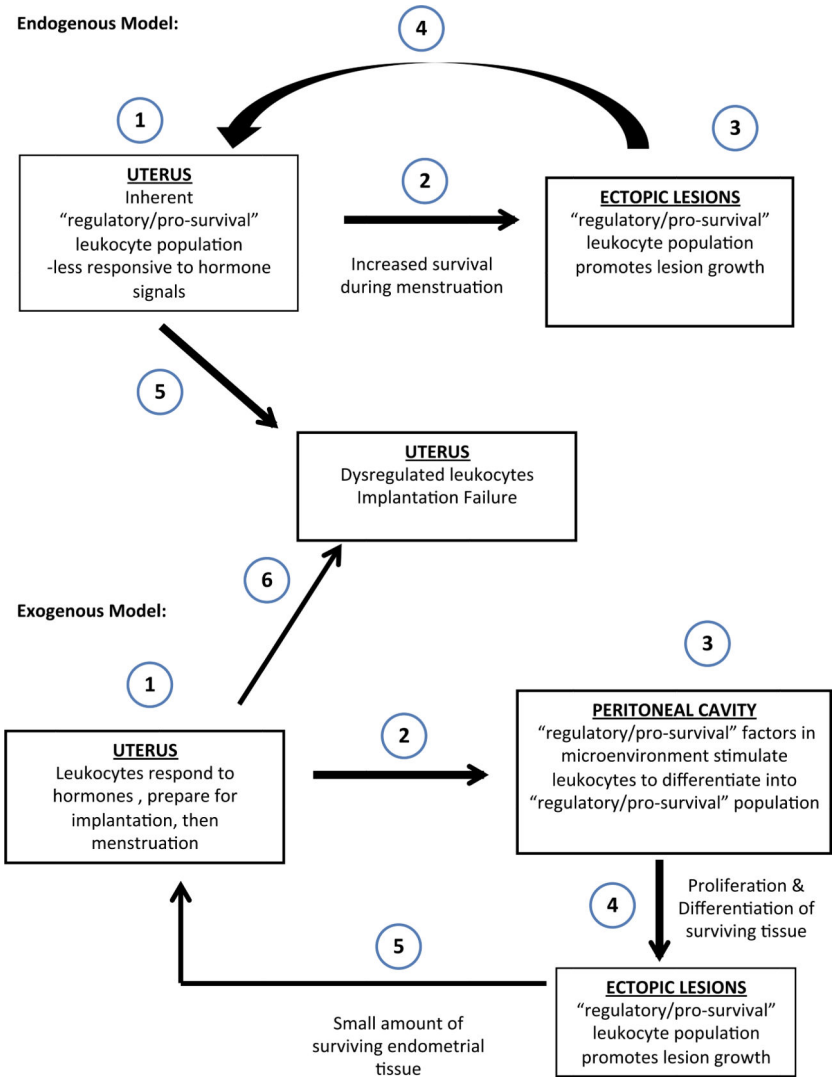

Fig. 1.

Models for development of ectopic lesions and their effect on eutopic endometrium. Inherited factors may lead to development of a regulatory environment in the eutopic endometrium (endogenous model) or a regulatory environment in the peritoneal cavity (exogenous model). Both result in survival of shed endometrial tissue and development of ectopic lesions. Cells and soluble factors from the lesions may then traffic to the eutopic endometrium and promote an environment that leads to implantation failure and continues development of the disease.