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Prospects for potential therapy targeting immune-associated factors in endometriosis (Review)

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Abstract. Endometriosis (EM) is a chronic inflammatory disease that is one of the most common causes of gynecological systemic lesions in women before menopause. The most representative histological feature of EM is that the endometrium appears outside of the uterine cavity, often in the ovary. Although it is generally accepted that the epithelial and stromal cells of the ectopic endometrium are not malignant, they still have numerous similarities to malignant tumors, including considerable changes to the immune microenvironment (immune monitoring disorder), the creation of a specific hormone environment, high levels of oxidative stress, chronic inflammation and abnormal immune cell regulation. The pathogenesis of EM is not fully understood, which makes it difficult to identify specific biomarkers and potential therapeutic targets for early disease diagnosis and effective treatment. However, considerable progress has been made in this field over the past few decades. The purpose of the present review is to summarize the confirmed and potential biomarkers for EM, and to identify potential therapeutic targets based on changes in immunological factors (including natural killer cells, macrophages, the complement system, miRNA and P-selectin) in the ectopic endometrial tissue. It is hoped that this work can be used as the basis for identifying accurate diagnostic markers for EM and developing personalized immune-targeted therapy.

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1. Introduction

Endometriosis (EM) is a common disease of the female reproductive system in which endometrial tissue exists outside of the uterus. Current estimates suggest that the total number of women diagnosed with endometriosis worldwide is as high as 190 million (1,2). These ectopic endometrial tissues are usually found in the ovary, ovarian fossa, uterosacral ligament, and both the anterior and posterior compartments of the pelvis (3-5). Although EM is recognized as benign cell proliferation, it has characteristics similar to malignant tumors, such as progressive and invasive growth, genetic instability, excessive proliferation, estrogen-dependent growth and a tendency to metastasize (6). Studies over the past few decades have shown that there is a correlation between EM and susceptibility to a variety of malignancies, including endometrioid carcinoma, clear cell carcinoma and low-grade serous ovarian cancer (7,8). It has also been reported that multifocal EM often presents with clonal growth and an increased mutation load, which are similar characteristics to cancer (9). The ectopic epithelial cells of patients with advanced EM even show signs of atypical hyperplasia. Typical changes of EM, as reported in the studies by Czernobilsky and Morris (10), and LeGrenade and Silverberg (11), which are used as diagnostic criteria in most studies (6), include three features: i) Enlarged hyperchromatic or morbid nuclei with moderate to considerable pleomorphism; ii) increased nuclear:cytoplasmic ratio; and iii) crowding, stratification or tufting of cells. This indicates that EM may be a transitional form between a benign and malignant lesion.

A delayed clinical diagnosis of EM is common (12), which may lead to disease-associated deterioration, a poor prognosis and an increased recurrence rate. Patients with at

least one of the following symptoms may be candidates for an EM diagnosis: i) Dysmenorrhea that affects daily activities and life; ii) chronic pelvic pain and pain during or after intercourse; iii) gastrointestinal symptoms associated with the menstrual cycle (especially painful bowel movements); iv) urinary symptoms associated with the menstrual cycle (particularly hematuria or painful urination); and v) infertility in combination with at least one of the aforementioned symptoms.

The actual prevalence of EM among adult women remains unknown (13). The prevalence of EM in infertile women is 1.5-5%, and the prevalence of EM in women who undergo sterilization can range from 2-68% (14). For women who suffer from pelvic pain, the rate of identifying EM lesions during laparoscopy can range from 15 to 75% (15). EM invading other organs is often accompanied by specific symptoms, such as frequent bowel movements, constipation, hematochezia, painful bowel movements or bowel cramps, in the setting of intestinal EM (16). Other ancillary examinations, including ultrasound, MRI, cystoscopy, enteroscopy, transintestinal ultrasound and biopsy are frequently used in the clinical diagnosis of EM (16-19). No specific biomarker is currently capable of diagnosing EM.

The general purpose of EM therapy is to reduce and eliminate lesions and pain, improve and promote fertility, and reduce and avoid recurrence. Treatments should strictly follow the following principles: i) Clinical problem-oriented, patient-centered, comprehensive long-term management according to different age stages; ii) empirical drug therapy should be started as early as possible based on the clinical diagnosis; iii) the timing of surgery should be standardized and attention should be paid to the protection of ovarian function and fertility to maximize the benefits of surgery; iv) after conservative surgery, long-term drug management and comprehensive treatment should be used to prevent recurrence; and v) regular review is recommended. Patients with considerable risk factors for malignant transformation should receive additional attention to avoid a missed or delayed diagnosis.

Medical and surgical treatments are both common in the clinical management of EM (17). Long-term management of EM should maximize the efficacy of drug therapies by suppressing the activity and differentiation of lymphocytes, forming an *in vivo* hypoestrogenic environment and relieving pain (17,20). Five main types of drugs are included in the common medical management of EM: Non-steroidal anti-inflammatory drugs, progestins, combined oral contraceptives (COCs), gonadotropin-releasing hormone agonists (GnRH-a) and traditional Chinese medicine (21-23). Surgical treatment is recommended for patients who are infertile, who have adnexal cysts with a diameter >4 cm and who are unresponsive to medical treatment (24). Different types of surgery are carried out according to the preoperative evaluation and personal needs of the patient. Lesion resection (or conservative surgery), which is mainly conducted laparoscopically, preserves reproductive function (17,25). Hysterectomy is suitable for patients with severe symptoms or those at a high risk of recurrence, who have no reproductive requirements but wish to preserve their ovarian endocrine function. Hysterectomy and bilateral adnexectomy are recommended for patients with severe symptoms, a high risk of recurrence, no reproductive requirements and who are unresponsive to drug therapies (25). Since EM is prone to relapse and has a considerable impact on female fertility (26), preserving the reproductive ability and endocrine function of the ovaries and uterus, and preventing disease recurrence should be the top priority of EM management. However, a more thorough understanding and interpretation of the pathogenesis and etiology of EM is required to make the most of current medical treatments and to innovate new techniques for achieving an improved outcome.

The origin and pathogenesis of EM remains unclear. At present, the most commonly accepted theory is Sampson's retrograde menstruation theory, in which menstrual debris may be transferred to the peritoneal cavity through the reverse peristalsis of the fallopian tube (27,28). However, it is argued that retrograde menstruation is widespread in healthy women, and that retrograde menstruation alone does not necessarily lead to EM (29).

Etiological study of EM shows that it is a multifactorial disease. Pathological studies have shown that the immune microenvironment in the ectopic endometrium is considerably altered. Researchers found that there were considerable abnormalities in the immune surveillance system of ectopic endometrial tissue, which permits its implantation into the peritoneal cavity without clearance by immune tissue (30-32). Ectopic endometrial tissue not only promotes an oxidative stress response and chronic inflammation in the ectopic areas, but also promotes the aggregation and activation of macrophages, thus inducing the production and release of the growth factors, angiogenic factors and inflammatory cytokines secreted by macrophages. This may also be the reason why EM effects fusion of the spermatocyte and oocyte, embryo implantation and embryo development, resulting in reproductive disorders (33-35).

The ectopic endometrium also has an abnormal inflammatory hormone environment that is characterized by local estrogen levels that are increased several-fold when compared to that of the peripheral blood. This results in a series of cellular and cytokine responses that include cell proliferation and the release of various immune and inflammatory factors, such as tumor necrosis factor-α (TNF-α), transforming growth factor (TGF)-β1, interleukin (IL)-1, IL-6, IL-8 and IL-10 (36). Possible subsequent clinical outcomes include an acute inflammatory response, pain (including dysmenorrhea, chronic pelvic pain and dyspareunia), gastrointestinal symptoms (painful bowel movements) and urinary symptoms (hematuria) that are associated with the menstrual cycle, as well as EM-associated infertility (35,37-40) (Fig. 1).

Researchers therefore hypothesize that EM is not only a gynecological disease, but also a chronic inflammatory systemic disease that is associated with immunity. Findings that support this include increases in non-specific inflammatory markers, such as CA-125 and CRP, and the presence of antinuclear antibodies in the patient's peripheral blood (40-43). Immune cells and their products are typically able to detect and eliminate abnormal cells (44). Considerable changes have been found in the regulation of various immune cells in patients with EM, including downregulation of the cytotoxicity of natural killer (NK) cells, infiltration and activation of macrophages, infiltration and dysfunction of T and B lymphocytes,

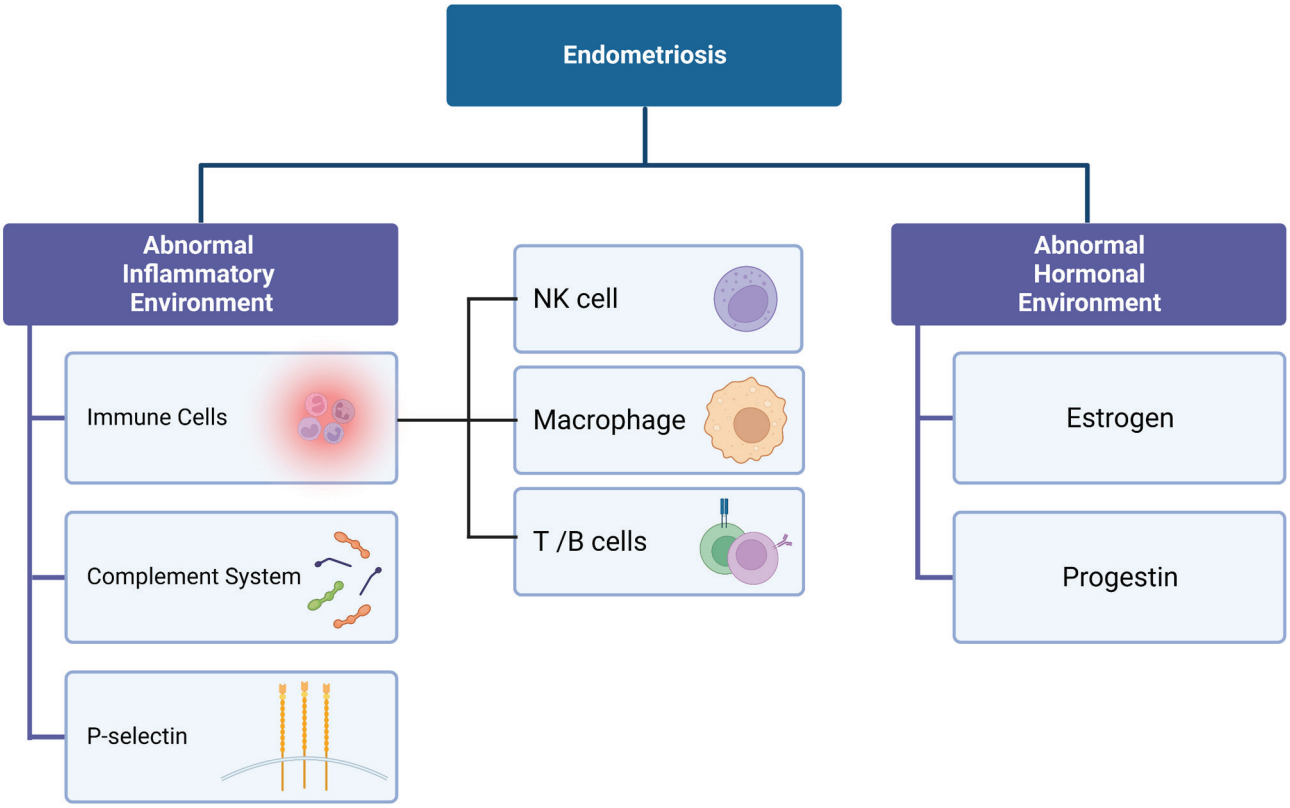

Figure 1. Changes in the microenvironment of EM. Alterations within the EM microenvironment can be categorized into two main classes. The first class pertains to the abnormal inflammatory environment, which encompasses immune cells, the complement system and P-selectin. The second class involves the abnormal hormonal environment, with particular emphasis on estrogen and progestin. NK, natural killer.

activation of polyclonal B lymphocytes, impaired apoptosis, dysfunction of Th1 and B cells, and translocation of T regulatory cells (45-48). This abnormal immune cell regulation provides various targets for EM therapies. The inhibition of NK cells and the abnormal activation of macrophages are considered key factors in the progression of EM, and therefore potential targets for EM immunotherapy (49-51). In addition to the requirement for a favorable immune environment for the survival of ectopic endometrial tissue, hypoxia stress and adhesiveness are two additional obstacles for the successful implantation of ectopic endometrial tissue. In a previous study, increased levels of hypoxia inducible factor-1α (HIF-1α) were observed in ectopic endometrial tissues compared with those in normal endometrium (52). HIF-1α is considered the best biomarker for tissue hypoxia and has an important role in the hypoxic response to ectopic tissues, including cell adhesion, angiogenesis and cell proliferation (53). As predicted, the inhibition of HIF-1α production in a mouse model of EM induced by suturing slices of uterus to intestinal mesenteric vessels could inhibit EM progression (54). HIF-1α could therefore function as the molecular target of EM therapy. Previous studies have shown that hypoxia promotes the release of angiogenic factors, such as vascular endothelial growth factor (VEGF-A), and inflammatory cytokines, such as IL-1β, TNF, TGF-β and IL-8 (55-57). Some responses to hypoxia interact with and regulate the activity of certain types of immune cells. For example, hypoxia-induced TGF-β elevation in the peritoneal fluid of patients with EM was found to be associated with the suppression of NK cells (58). Activation of macrophages in the peritoneal fluid in response to hypoxia was also found to be associated with and possibly contributed to the reduced cytotoxicity of NK cells in patients with EM (59). The programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway was also found to be involved in the immune tolerance that contributes to the pathogenesis of EM (60). These results suggest that not only are NK cells potential therapeutic targets for EM, but that immune checkpoint blocking to avoid NK cell immunosuppression can be used to investigate alternative methods for treating EM.

The normal endometrium contains various immune cells that change in distribution and number throughout the menstrual cycle (61). The normal periodic changes in immune cells are dysregulated in EM, considerably impacting both the composition and function of immune cells. Lymphocytes and macrophages are the main components in the lesion microenvironment. Compared with healthy women, women with EM have a considerably increased proportion of peritoneal macrophages in the peritoneal fluid, which contributes to the proliferation and survival of ectopic endometrial cells (62). The levels of the main components of potential biomarkers in the peritoneal fluid are also increased in the setting of EM, including phosphatidylcholine, phenylalanine isoleucine, glycidyl deproteinization, placental protein 14, midkine, IL-8 and osteoprotegerin (59,60). Changes in the composition and proportion of certain molecules in the peritoneal fluid may lead to impaired T cell and NK cell cytotoxicity (47,63). The aforementioned changes in the immune environment help to establish an immunosuppressive microenvironment that is

conducive to the proliferation and invasion of epithelial cells and stromal cells into the ectopic endometrial tissue, and supports angiogenesis in the ectopic microenvironment (64,65).

The treatment for EM includes surgical resection and hormone therapy, both of which have advantages and disadvantages. Surgical treatment can remove the ectopic cyst and identify the location of the lesion. However, surgical resection without long-term medical treatment has a high EM recurrence rate and a decline in ovarian function. Medical therapy can slow the progression of EM to a certain extent, delay the need for surgery and avoid surgical complications. However, it cannot clarify the nature of the lesion or effectively reduce the lesion size. As specific targeted immunotherapy is usually not universal and there is not enough experimental validation, it may be potentially effective in this domain and deserves more attention (66,67).

2. NK cells

Function and regulation of NK cells. NK cells are large granular lymphocytes that are characterized by $CD56^{+}$, $CD16^{+/-}$ and $CD57^{+/-}$ expression, and positivity for natural cytotoxicity trigger receptor 1 (NCR1) , otherwise known as CD335, but not CD3 or surface T cell receptor (68,69).

NK cells can be divided by their expression level of CD56 into cd56bright and cd56dim, which have increased and reduced expression levels of CD56, respectively. Cd56bright NK cells produce more abundant cytokines, while cd56dim NK cells have increased cytotoxicity and increased expression levels of FC γ receptor III (fcgr3), also known as CD16 (70,71). NK cells spontaneously recognize and eliminate infected, ectopic, tumorigenic and stress responsive cells so as to automatically monitor for viral infections, ectopic tissue and malignant cells (72-74). Repeated exposure to the same target results in increased accumulation of NK cells and the production of a specific recall response by NK cells that is characterized by the enhancement of the functional activity of NK cells against the target (75-77). The binding of inhibitory killer cell immunoglobulin-like receptor (KIR) on NK cells with MHC class 1 or human leukocyte antigen (HLA)-1 (KIR/HLA-1) inhibits the activation of NK cells and allow for further intrinsic interactions. KIR therefore has an important role in distinguishing autologous cells from diseased and foreign cells to avoid non-selective killing of autologous healthy cells (78,79). The maturation and cytotoxic function of NK cells is based on the interactions between KIR and autologous MHC molecules, which is called licensing (80). Once licensed and functionally mature, NK cells are inhibited by inhibitory receptors that bind to the autologous MHC. Cells without MHC class 1 expression will be eliminated by activated NK cells (81). If NK cells are not stimulated by interaction with autologous MHC they may lose their normal function (82). However, the inhibition of KIRs and MHC is not absolute in mature NK cells and can also be eliminated or offset by a much stronger active stimulator. Other MHC receptors are also involved in NK cell cytotoxicity regulation against target cells, such as leukocyte immunoglobulin-like receptor subfamily B (LILRB) and natural killer group protein 2 (NKG2) (83-85).

Among the receptors that activate NK cells, FCGR3, which is expressed in almost all NK cells, is key for antibody dependent cytotoxicity. FCGR3 expression levels alone are sufficient to induce interferon γ and TNF, making it is one of the most effective activating receptors of NK cells. Other receptors that can activate NK cell cytotoxicity include NCRs, which are divided into NCR1, NCR2 and NCR3 (or NKp46, NKp44 and NKp30, respectively) (86).

In addition to licensing through the interaction between receptors on the surface of NK cells and the autoantibodies of the body, exposure to cytokines is also essential to activate the cytotoxicity of immature NK cells and promote cytokine secretion (87). IL-2 and IL-15 secretion by macrophages can activate and trigger the maturation of NK cells and promote their proliferation (88-90). Simultaneous exposure to IL-12 and IL-18 is not only able to activate NK cells, but can promote IFN-γ secretion (91,92). Conversely, increased interferon secretion can also enhance the cytotoxicity of NK cells, such as the anti-tumor response of NK cells that is mediated by the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway activation (93). Activated NK cells can induce apoptosis by releasing cytolytic particles against target cells. They can also by cytotoxic to target cells through a Fas L-mediated mechanism with the help of the CD95 receptors on the surface of target cells (94,95).

NK cells in EM. Several reports have shown that NK cells in patients with EM have reduced abilities both in clearing out of ectopic endometrium and in participating in local and systemic immunity, which creates a favorable environment for the survival and growth of ectopic endometrial tissue (96-98). NK cytotoxicity decreases not only in ectopic endometrial tissue, but also in the peripheral blood and peritoneal fluid (99).

Decreased NK cytotoxicity is currently debated, as to date, studies on this topic have not adequately shown this cytotoxicity to occur (48,100,101). It has been speculated that the upregulation of NK cell inhibitory receptors and the downregulation of stimulatory receptors in ectopic endometrium may be caused by cytokines such as IL-2, IFNs and TGF-β. This indicates that cytokine therapy targeting NK cell inhibitory or stimulatory receptors is feasible (102,103). Most studies show that the proportion of NK cells decreases in patients with EM. However, there are also studies showing that the proportion of NK cells in patients with EM increases when compared with that in healthy controls (104,105). These results suggest that the decreased NK cytotoxicity in patients with EM is not the result of decreased NK cell infiltration, but rather the abnormal expression level of NK cell activation receptor and/or inhibition receptor. However, only the upregulation of NK cell inhibitory receptors is supported by current research, while the regulation of stimulatory receptors remains unclear due to the lack of studies and considerable results.

Overexpression of inhibitory receptors is considered vital for modulating immune evasion and maintaining immune tolerance in EM. Increased levels of HLA-1 in the glandular and stromal cells of endometrial tissue was observed in the study by Vernet-Tomas Mdel *et al* (106), which may result in increased resistance to NK cytolysis in patients with EM (106). The case-control study by Wu *et al* (107) finds that the levels of KIR in the peritoneal NK cells of patients with

EM also increased (including NKB1 and EB6), thus further reducing the cytotoxicity of NK cells (107). Overexpression of other inhibitory receptors and their ligands were observed in patients with EM, including the inhibitory receptors KIR2DL1, CD94/NKG2a and LILRB1 on peritoneal NK cells, and their separate endogenous ligands HLA-C, HLA-E and HLA-G (108-110). The altered presence and distinct combined presence of different KIR genes contributes to a unique genetic background of patients with EM. It should be noted that not all KIR/HLA binding promotes the development of EM. For example, receptor KIR2DS5 in combination with its ligand HLA-C C2 has a protective effect against EM (111).

Decreased expression levels of NKG2D, a stimulatory receptor of NK cells, was also reported in patients with EM (112). It is plausible that the downregulation of NKG2D is the result of increased levels of TGF-β and ectopic endometrial tissue-derived IL-15 (113,114). However, the ligands for NKG2D, including MHC class-I chain-associated proteins (MIC)A and B that were upregulated in the peritoneal fluid of patients with EM (115), paradoxically exert an inhibitory effect on NK cells (116,117). The precise mechanism behind how the regulation of NK cell stimulatory receptors influences the pathogenesis of EM requires further verification and examination.

IL-12 can regulate the immune recognition of NK cells in the endometrium. IL-12 is composed of two heterologous polypeptide chains, p40 and p35. A study found that the concentration of IL-12 in patients with EM is similar compared with that of healthy controls. However, increased levels of free p40 in the peritoneal fluid of these patients indicated that overexpression of the p40 subunit alone could reduce the cytotoxicity induced by IL-12 (118). The ratio of FCGR3-negative NK cells to FCGR3-positive NK cells in the peritoneal cavity of patients with EM was increased (119). Based on these findings, the increased expression levels of inhibitory receptors and ligands has a key role in the decline of NK cytotoxicity.

Platelets also regulate the function of NK cells (111). Platelets release TGF-β during retrograde menstruation in patients with EM, thereby suppressing the expression level of a stimulatory receptor of NK cells, NKG2D and reducing their cytotoxicity (Fig. 2) (120-123).

NK cell-associated therapeutic targets for EM. Studies on the changes and mechanisms of NK cells in patients with EM provide a solid experimental basis for the targeted treatment of EM. The present focus of immunotherapy targeting NK cells is to restore their cytotoxicity. To reach this goal, three possible aspects should be considered: i) Blocking inhibitory receptors; ii) anti-inhibitory or stimulatory cytokine therapy; and iii) immune checkpoint therapy.

KIR2DL1, LILRB1/2 and CD94/NKG2a are inhibitory receptors that are overexpressed in the NK cells of women with EM. The ability to interfere with the binding of the inhibitory receptors and their ligands to improve the cytotoxicity of NK cells has been tested by multiple studies (124,125). Disruption of the inhibitory receptors on NK cells contributing to enhanced cytotoxicity was found in a human cell model treated with 5-aza-2'-deoxycytidine reported by Binyamin *et al* (124) in 2008. The study observed increased NK cell cytotoxicity when the inhibitor KIR2DL1 was applied to the NK cells of a healthy woman. It was also observed that blocking KIR2DL1 can enhance the effects of rituximab (an anti-CD20 monoclonal antibody known to recruit the immune system to attack and kill B cells) by increasing the cytotoxicity of NK cells (124,126). The study by Andre *et al* (125) targeted NKG2A on NK cells with monalizumab combined with cetuximab (an EGFR inhibitor) in patients with head and neck carcinoma, resulting in increased NK cell cytotoxicity (125). Whilst neither of these studies were based on EM, this blocking of inhibitory receptors therapy may be a promising treatment for EM and has been shown to be effective against some malignancies (125,127); however, further studies on their role in EM are required to make conclusive statements.

Previous studies tried to identify cytokines that affect the regulation of NK cell activity as new targets for immunotherapy. Some ILs (such as IL-2 and IL-12) and IFNs are NK cell stimulative cytokines. Intraperitoneal injection of IL-2 in surgically implanted EM rat models was found to be capable of recruiting leukocytes into EM lesions and reducing lesion size (128,129). However, existing studies on the therapeutic effects of IL-2 on EM are based in animal models, therefore, further studies and analysis are needed on the applicability to human patients. IL-12 is another important NK cell stimulative cytokine. Researchers pretreated NK cells with an IL-12 heterodimer to reduce the ratio of free p40 to IL-12 and enhance the cytotoxicity of NK cells in ectopic endometrial tissue, resulting in suppressed development of ectopic endometrial tissue. IL-12 is therefore considered a potential specific target for correcting the increase in free p40 levels in patients with EM (118). Type I IFNs, which include IFN-α2b, IFN-β1a and type II IFN (IFN-γ), can activate NK cells and enhance their cytotoxicity. However, to the best of our knowledge, no work has studied the feasibility of using the NK cell activating effects of IFNs to treat EM. The study by Dicitore *et al* (130) showed that IFN-β1a is superior to IFN-α2b at inhibiting the proliferation and migratory activities of endometrial stromal cells.

A case-control study by Wu *et al* (131) found that treatment with GnRH-a could restore the damaged immune function of the peritoneal fluid in patients with EM, and proposed their hypothesis according to their findings (131). In this study, women with EM who used GnRH-a long-term were found to have increased levels of the $CD3^-CD69^+$ subpopulation of peripheral blood mononuclear cells and the $CD3^+CD69^+/CD3^+CD24^+$ subpopulation of activated T cells. It was suggested that the increased level of activated T cells induced by GnRH-a secreted increased levels of IL-2 and IFN-γ, which led to restoration of NK cell activity in the peritoneal fluid.

TGF-β suppresses the cytotoxicity of NK cells and the function of other immune cells (132,133). TGF-β secretion is upregulated in women with EM and is considered important to EM pathogenesis (134,135). Anti-TGF-β therapies are currently being evaluated clinically as treatments for malignancies and other diseases, such as diabetes. However, the results are generally unsatisfactory, reporting non-responsiveness and potential systematic side effects (136,137). There are also concerns that anti-TGF-β therapies would cause systematic suppression and result in severe systematic side effects due to the important role that TGF-β has in multiple vital signaling pathways, such as cell proliferation

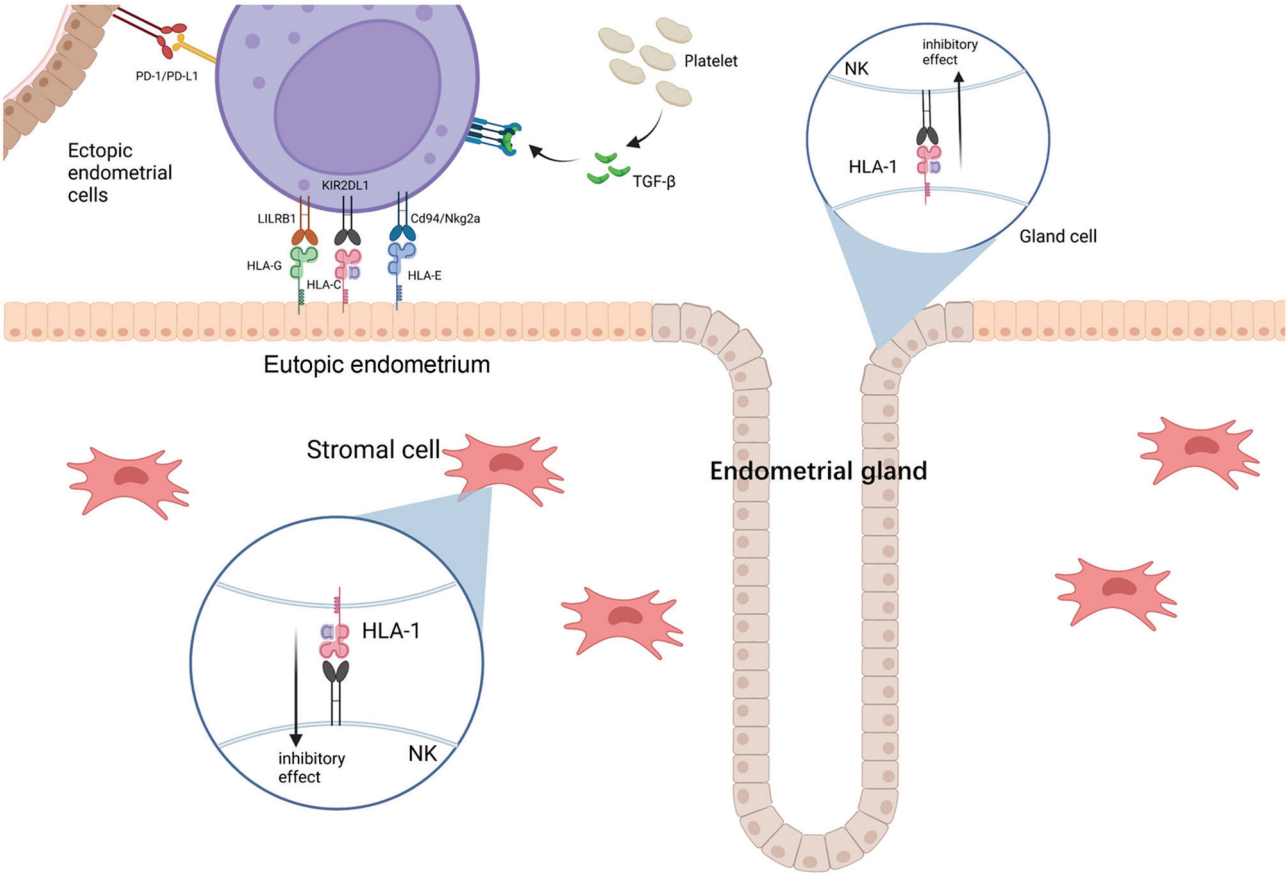

Figure 2. Regulation of NK cells in the EM environment. In patients with EM, the expression of HLA-1 in the stromal cells and glandular cells of eutopic endometrium is elevated. After binding with NK cells, it produces an inhibitory effect, which may lead to an enhanced tolerance of EM to NK cells. Meanwhile, the levels of inhibitory receptors (LILRB1, KIR2DL1 and Cd94/Nkg2a) on peritoneal NK cells and their endogenous ligands (HLA-G, HLA-C and HLA-E) are increased in patients with EM. During the retrograde menstruation of patients with EM, platelets release TGF-β, inhibiting the expression of the NK cell-stimulating receptor NKG2D and reducing its cytotoxicity. In addition, the expression of PD-L1 in ectopic endometrial cells is increased, which inhibits NK cells through the PD-1/PD-L1 axis. HLA, human leukocyte antigen; NK, natural killer; NKG2a, immune inhibitory receptor natural killer group 2 member A; LILRB1, leukocyte immunoglobulin-like receptor subfamily B member 1; PD-1, programmed death 1; PD-L1, programmed death-ligand 1; KIR2DL1, killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 1; EM, endometriosis.

and differentiation. *In vitro* and *in vivo* studies are needed to further study anti-TGF-β therapy for EM.

Other immunotherapies may restore NK cell function in EM, most of which are based on immunotherapy models of other diseases. In 2004, the study by Clayton *et al* (138) first proposed the possibility of using *Mycobacterium* to restore NK cell activity in EM (138). However, the hypothesis was only supported by *in vitro* studies and further verification is required.

Immune checkpoint blocks (ICBs) are also new immunotherapies that researchers are currently evaluating. PD-1/PD-L1 pathway-associated inhibitors are a type of checkpoint blocking therapy. Previous studies have reported increased PD-1 expression levels in the peripheral blood cells of patients with EM, and increased PD-L1 expression levels in both the ectopic and non-ectopic endometrial tissues of patients with EM (139,140). This indicates that the peripheral tolerance caused by PD-1/PD-L1-induced T cell suppression may contribute to the immune abnormalities noted in EM. ICB therapy using PD-1/PD-L1 inhibitors is a promising treatment for preventing immune tolerance to EM (141-143). However, studies have reported that PD-1/PD-L1 inhibitor treatment can lead to adverse reactions in a variety of tissues and organs throughout the body. The use of ICBs in the treatment of EM should therefore be carefully selected, and inhibitors with the strongest specificity for EM should be utilized (144,145). In addition to ICB therapy, the use of genetically modified NK cells, such as chimeric antigen receptor (CAR)-NK cells, in tumor immunotherapy has also attracted increased attention (146-148). However, engineering a CAR-NK structure requires a biomarker specifically expressed on the surface of ectopic endometrial cells, which, to the best of our knowledge, has not yet been discovered.

Although the aforementioned targets for the treatment of EM have been supported in theory by *in vitro* and animal experiments, limited clinical trials have been reported.

Obstacles and future prospects. The exact mechanism behind how immunosuppression in ectopic endometrial tissue and its environment damages the cytotoxicity of NK cells is unclear, which makes it difficult to identify an appropriate immunotherapy target. Three main specific inhibitory NK cell receptor families have been identified: KIR, LILRB and NKG2. To the best of our knowledge, there are no reports on the inhibition of these receptor/ligand interactions. Cytokine therapy and the upregulation of associated activated receptors also requires

further research. The possibility of utilizing immunotherapy in the treatment of EM needs further analysis due to the lack of tissue/cell specificity, which results in systemic side effects. It requires investigation on the epigenic differences between the ectopic and eutopic cells to develop treatments with increased specificity.

It should be noted that whether enhanced NK cell cytotoxicity is associated with abortion is debatable (149,150). Further examinations and analyses are needed before NK cell treatment can enter clinical research.

3. Macrophages

Phenotypes and function. Macrophages are a late differentiation cell type of the mononuclear-phagocyte system, which have an important role in both the non-specific and specific immune response. Macrophages were previously considered to be solely derived from blood monocytes, which are widely distributed and participate in the innate immunity of the body (151). This notion has changed due to the discovery of macrophages derived from and residing in specific tissues without the participation of circulating monocytes (152). Macrophages can be polarized into different directions based on the effects of different microenvironments and stimulating factors. Based on the surface markers of polarized macrophages and their functions, polarized macrophages can be categorized into two types: Classically activated macrophages (M1) and alternatively activated macrophages (M2) (153,154). M1 has a pro-inflammatory effect on the early stages of inflammation, phagocytizes and digests foreign pathogens, secretes pro-inflammatory factors, activates the T cell-dependent immune response and promotes the Th1 immune response. M2 can promote tissue repair and wound healing, regulates the Th2 immune response and contributes to disease recovery during the later stage of inflammation, which results in an anti-inflammatory effect (153,154).

There are two types of macrophages in the female pelvis: Endometrial and peritoneal. Endometrial macrophages (eMs) are involved in triggering and regulating the process of endometrial breakdown, and the subsequent repair of the endometrial functional layer by facilitating cell proliferation and angiogenesis (155,156). eMs function in the following three ways: i) Production and release of VEGF to promote angiogenesis; ii) participation in triggering and controlling the shedding process; and iii) facilitating and rebuilding the functional layer (157). Peritoneal macrophages (pMs) are distributed in ectopic endometrial tissues outside of the reproductive tract. The increased macrophages in patients with EM are mainly pMs. pMs have an immune monitoring role on the peritoneal surface. pMs can be classified into resident pMs and monocyte-derived pMs of bone marrow origin (158,159).

Based on the differences in MHCII and F4/80 expression levels, pMs can be divided into two phenotypes: Big, tissue-resident pMs and small, monocyte-derived pMs. Both types of macrophages can be either polarized into M1, which is pro-inflammatory, or M2, which is anti-inflammatory, depending on the stimulation of pathogen-associated molecular patterns (51). The pro-inflammatory M1 phenotype of pMs, similar to the classification of helper T cells, is activated mainly through the activation of IFN-γ, LPS, TNF-α or a combination of the three. The anti-inflammatory M2 phenotype of pM is mainly activated by IL-1, IL-10 and IL-13. The polarization of pMs produces corresponding molecular markers, which allows researchers to detect the regulation of macrophages (160-162). Another type of macrophage, tumor-associated macrophage, has a role in the nutrition and angiogenesis of patients with EM and endometrial cancer (Fig. 3) (64).

Macrophages in EM. Although the number and activation of pMs in patients with EM are increased, the phagocytic capacity of these pMs is still unable to remove the ectopic endometrial tissue debris. pMs obtained from women with EM show a reduced capacity for phagocytosis due to the decreased expression level and activity of matrix metalloproteinase-9, which is regulated by prostaglandin E2 (PGE2) and is the enzyme that is necessary in the degradation of the extracellular matrix (163-165).

Ectopic endometrial tissue is in a hormonal environment that contains abnormal concentrations of estrogen and androgens. The secretion of C-C motif chemokine ligand 2 (CCL2) by endometrial stromal cells is upregulated in the ectopic milieu, which has been confirmed to be mediated by estrogen (166). CCL2 mediates the polarization of macrophages to M2 instead of M1 (167). The abnormal EM environment also promotes the elevation of distinct anti-inflammatory phenotypes of macrophages, forming an immunosuppressive microenvironment by stimulating the proliferation of epithelial and stromal cells in endometriotic foci, and promoting angiogenesis (168). However, chronic inflammation is still observed in the lesion microenvironment. It could be possible that the upregulation of M2 is compensatory, induced by persistent inflammation and tissue repair. According to the macrophage depletion study by Bacci *et al* (169), anti-inflammatory M2 induced by macrophage colony-stimulating factor and IL-10 is considered to be of importance to the growth and development of ectopic EM tissue, while pro-inflammatory M1 induced by IFN-γ is capable of eliminating the ectopic tissue (169). The phenotypic plasticity of pMs makes it possible to investigate potential therapeutic targets for EM based on the suppression of the M2 phenotype in pMs or the activation of the M1 phenotype. The suppression of M2 polarization has already been proposed as chemical therapy for colon tumors, such as by using ovatodiolide to prevent the polarization of M2 tumor-associated macrophages (170).

Estrogen receptors on macrophages can be classified into surface receptors and nuclear receptors. Estrogen nuclear receptors can be divided into ER-α (ER1) and ER-β (ER2). ER2 promotes inflammation and disease progression by increasing the production of inflammatory cytokines, including IL-1β and IL-6 (171,172). IL-6 mediates the recruitment of monocytes and their differentiation into macrophages, which contributes to the increased macrophage infiltration into the EM lesions. ER2 also inhibits apoptosis by interacting with the NLRP3 sensor, caspase 1 and apoptosis signal regulated kinase-1 (173). However, chloroindazole, an ER2 ligand developed in 2015, can suppress inflammation and angiogenesis within the EM lesion, thereby suppressing EM progression (174). These data indicate that the activation of ER2 can also be anti-inflammatory and can serve as a possible target for EM treatment.

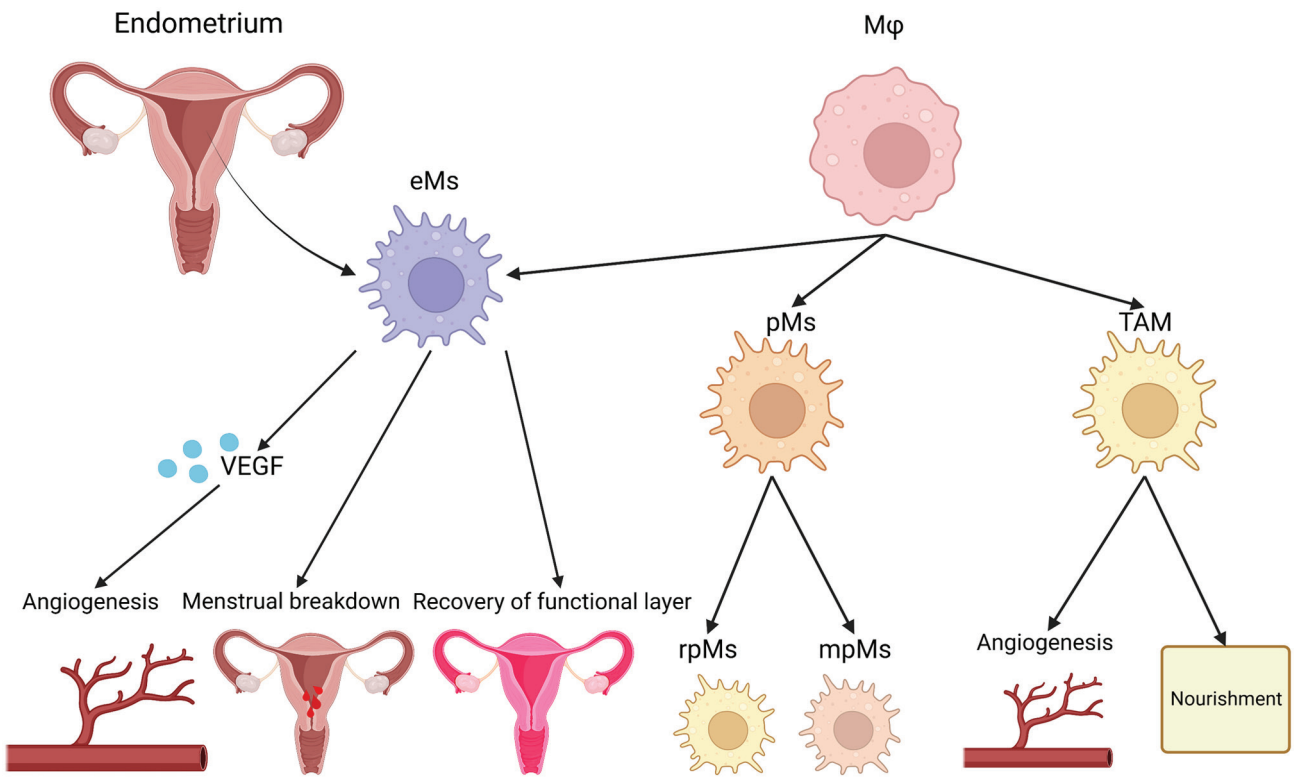

Figure 3. Phenotypes and functions of macrophages. In the female pelvis, two distinct types of macrophages exist: eMs and pMs. eMs possess the capacity to generate VEGF, which is instrumental in promoting angiogenesis. Additionally, eMs are implicated in the menstrual breakdown and recovery of functional layer. pMs are distributed within ectopic endometrial tissues outside the reproductive tract and fulfill an immune monitoring function on the peritoneal surface. pMs can be further categorized into rpMs and mpMs of bone marrow origin. Tumor-associated macrophages represent another macrophage phenotype, which are involved in nourishment and angiogenesis not only in patients with EM but also in endometrial cancer. eMs, endometrial macrophages; pMs peritoneal macrophages; VEGF, vascular endothelial growth factor; rpMs, resident macrophages; mpMs, monocyte-derived macrophages; EM, endometriosis; Mφ, macrophages.

ER1 has two main roles. Firstly, ER1 promotes the secretion of pro-inflammatory cytokines, such as IFN-1, contributing to the inflammatory response (175,176). Secondly, ER1 activation also inhibits the NF-κB pathway, which limits the extent of the inflammation (177,178).

Upregulation of ER2 expression levels and downregulation of ER1 expression levels in macrophages and endometrial stromal cells will result in an extremely low ratio of ER1:ER2. There are controversies on whether the influence the ER1 deficiency and ER2 overexpression have an inflammatory or anti-inflammatory effect on the EM environment due to the opposing findings of previous studies (172,179). Despite these controversies, the consensus is that the dysregulation of estrogen and ERs contributes to inflammation in EM. The regulation of inflammatory pathways and immune cells by ERs and estrogen in endometriotic stromal cells will be discussed in further detail below.

Estrogen receptors on the cell surface are G protein-coupled ERs (GPERs), which are expressed on the surface of macrophages in this hormonal environment (180). GPERs are seven transmembrane-spanning receptors that bind to estrogen and mediate rapid non-genomic signaling pathways, such as the mitogen-activated protein kinases (MAPK) pathway and the phosphatidylinositide-3-kinases/Akt (PI3K/Akt) pathways, which can be initiated within seconds and rapidly induce a physiological response in target cells (181). GPER expression levels in macrophages within ectopic endometrium are increased, suggesting that this abnormality may be important to the regulation of the macrophage immune response (182). The roles of GPERs in EM have been gradually discovered and reported, making them a promising target for EM therapy. Activation of GPERs by their agonist G-1 can inhibit the secretion of TNF-α and IL-6 that was induced by LPS, resulting in an anti-inflammatory effect on GPER-expressing macrophages (183).

Continuously elevated estrogen levels also lead to the synthesis and secretion of inflammatory cytokines by macrophages, such as IL-1, IL-6 and TNF-α, which trigger a series of pro-inflammatory responses (173,184). Macrophages have a two-way response to estrogen: Upregulation of pro-inflammatory cytokines is induced by comparatively low concentrations of estrogen and inhibited by increased concentrations of estrogen (185). It has been hypothesized that the function of macrophages in ectopic endometrial tissue may be estrogen-dependent, and that estrogen may regulate the immune response through the GPERs and ERs of macrophages in ectopic endometrial tissue (182,186). These observations indicate that whether these estrogen-dependent events have a pro- or anti-inflammatory role on macrophages in EM depends on the types of ERs and the local concentration of estrogen within the lesion.

The chronic inflammatory environment in ectopic endometrial tissue triggers the secretion of inflammatory cytokines, such as IL-1β, IL-17A and TNF-α (187). Increased

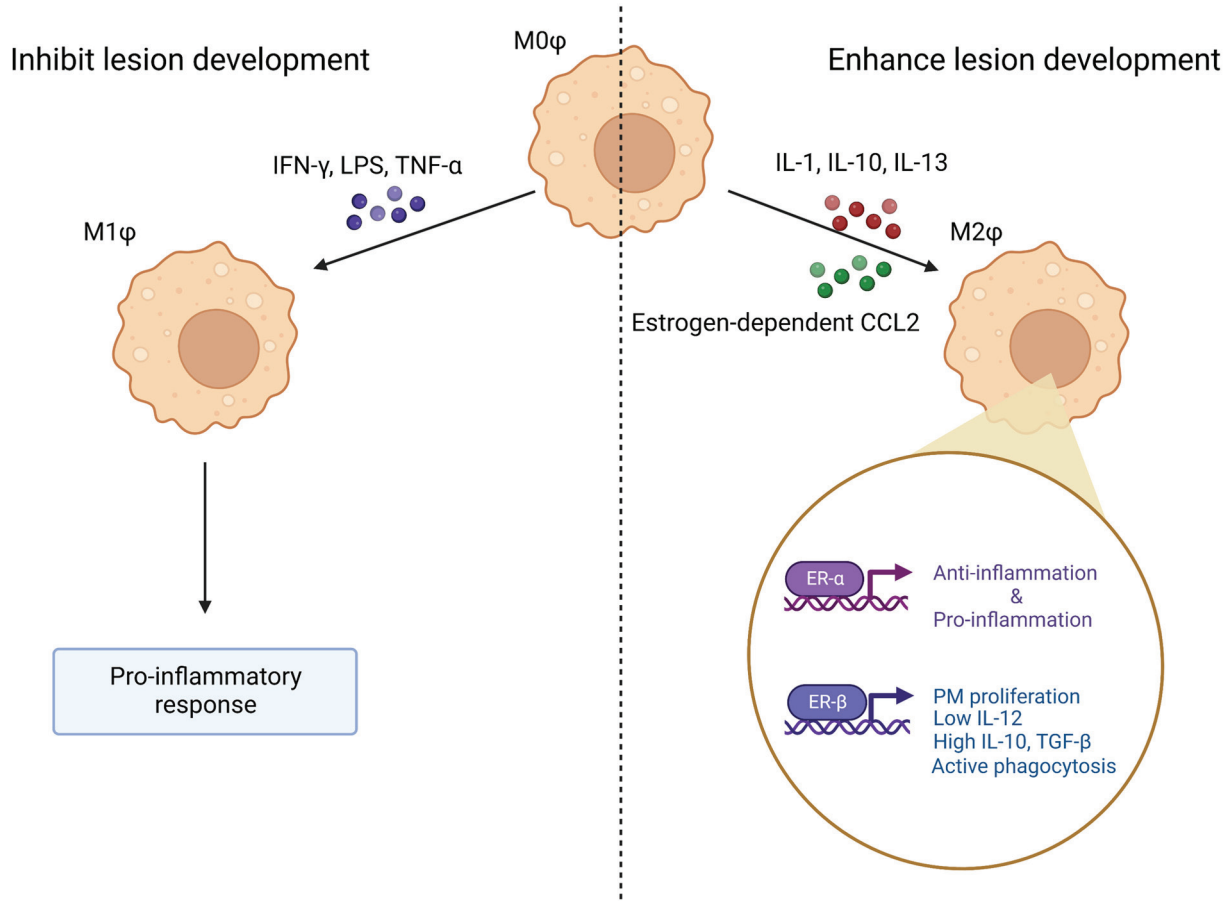

Figure 4. Polarization of macrophages and the response of estrogen. In EM, M0 macrophages transform into M1 macrophages under the action of IFN-γ, LPS and TNF-α. M1 macrophages have a pro-inflammatory response and can inhibit lesion development. M0 macrophages can transform into M2 macrophages under the action of IL-1, IL-10, IL-13 and estrogen-dependent CCL2. M2 macrophages have an anti-inflammatory effect and enhance lesion development. There are two estrogen nuclear receptors, ER-α and ER-β, in M2 macrophages. Activation of ER-α promotes the secretion of pro-inflammatory cytokines and promotes the inflammatory response. Meanwhile, the NF-κB pathway is also inhibited by the activation of ER-α, limiting the degree of inflammation. Activation of ER-β can lead to PM proliferation, low IL-12, high IL-10 and TGF-β, and active phagocytosis. EM, endometriosis; LPS, lipopolysaccharide; ER, estrogen receptor; IL, interleukin; TNF-α, tumor necrosis factor-α; CCL2, C-C motif chemokine ligand 2; M1ϕ, classically activated macrophages; M2φ, alternatively activated macrophages.

inflammatory cytokines can lead to the abnormal activation of the mTOR/PI3K signaling pathway, and the abnormal activation and proliferation of keratinocytes (188). Whether the same inference can be made on macrophages in EM requires further study. In addition, inflammatory cytokine IL-6 in inflamed tissue acts as a superior coordinator of protein synthesis capacity and cell growth rate by stimulating the translation of c-Myc mRNA, an oncogenic transcription factor that activates transcription via all three nuclear RNA polymerases. RNA polymerase I-associated transcription factors are recruited to rDNA by IL-6 when quiescent cells are stimulated to re-enter the cell cycle. Stimulated c-Myc mRNA will therefore eventually lead to an upregulation of rRNA transcription and enhanced proliferation of macrophages (189).

Macrophages are also involved in the induction of the immunosuppressive peritoneal environment in EM. IL-8 secreted by macrophages increases the expression level of Fas ligand (FasL) in endometrial cells, and the binding of FasL to Fas on T cells triggers apoptosis (190). It has been reported that the mRNA level of IL-8 in the peripheral blood and peritoneal fluid of patients with EM is considerably increased. The expression level of FasL on endometrial cells is also increased, which contributes to the formation of the immunosuppressed and immune tolerant microenvironment that is conducive to the adhesion of ectopic cells (191). Serum IL-8 levels have the potential to be an early indicator of EM (192). However, there seems to be little research assessing relevant immunotherapeutic targeting of Fas/FasL for EM. Other immunosuppressive cytokines are also secreted by macrophages in ectopic endometrial tissues, including IL-10 and TGF-β, leading to the inhibition of NK cells in the peritoneal cavity (Fig. 4) (59).

Similar to malignant tumors, the expression level of oncogenes and tumor suppressor genes in EM is considerably altered. Studies have shown that c-Myc, a recognized oncogene, is overexpressed in most patients with EM. It has been proposed that c-Myc also participates in the pathogenesis of EM (189,193).

In addition to the aforementioned inflammatory cytokines that have important roles in the pathogenesis of EM, Tie2-expressing macrophages in ectopic endometrial tissue inhibit endothelial cell apoptosis by preventing the caspase-3 activation of neovascular endothelial cells. This may also be used as a potential therapeutic target for EM (194).

EM is characterized by considerably increased levels of macrophage migration inhibitory factor (MIF), a multipotent protein that has a range of immune regulatory functions and is a key upstream regulator of both the non-specific and specific immune responses. During the onset of premenstrual syndrome, patients with EM have elevated MIF levels in the normal endometrium, early ectopic endometrium, peritoneal fluid and systemic circulation (195-198). Studies have shown that MIF and its specific inhibitors can be used not only to improve the accuracy of EM diagnosis, but also to develop new therapeutic strategies against EM. The study by Seeber *et al* (199) found that the combined use of MIF and factors such as CA-125, monocyte chemoattractant protein 1 and leptin, can improve the accuracy of EM diagnosis to 93% (199). The concentration of macrophages in the normal endometrium of patients with EM is considerably reduced when compared with that of healthy controls, which predisposes patients to a poor prognosis (200).

It has been suggested that abnormal macrophage regulation may also be associated with the various clinical features of EM. For example, the increased concentration of pMs may disturb normal fertilization and lead to infertility in women with EM (201). Decreased insulin-like growth factor-1 (IGF-1) production by macrophages may also be associated with pelvic pain associated with EM (202).

In conclusion, patients with EM have increased macrophage levels and activation mediated by the mTOR/PI3K signaling pathway, c-Myc oncogene expression levels, and its resulting ribosome biogenesis in EM lesions and peritoneal fluid. Macrophages that co-exist with ectopic EM cells *in vitro* are immunosuppressive and macrophages in the peritoneal fluid of women with EM exist as a mix of both pro-inflammatory and anti-inflammatory cells. Anti-inflammatory macrophages in peritoneal fluid, which are M2, promote the development of EM lesions, while pro-inflammatory macrophages, which are M1, are antagonistic. Increased concentrations of estrogen in the ectopic EM microenvironment promote re-polarization from M1 to M2, which further contributes to the growth of the lesion.

Macrophage-associated therapeutic targets. Several theories for immune-associated therapies targeting the upregulation of pMs in EM have been proposed. The main hypotheses regarding the upregulation of pMs in the peritoneal fluid of patients with EM include the estrogen dependency theory, the mTOR/PI3K signaling pathway theory, overexpression of the oncogene c-Myc, ribosome biogenesis and the overexpression of MIF. Several potential medication therapies for managing these etiologies have been proposed.

Regarding the estrogen dependency theory, estrogen replacement and other associated therapies are being investigated and introduced into clinical management. The estrogen replacement therapy is currently the most commonly used method for treating EM that can achieve complete ovarian suppression, and has been in use since it was first reported in 1948 (203). Low-doses of combined estrogen and progestin or progestin alone can effectively relieve the clinical symptoms of pelvic pain caused by EM, and can also reduce the adverse effects of low estrogen that are induced by GnRH agonists (204). However, GnRH therapy can lead to several clinical side effects, including increased follicular development (205).

In addition to the estrogen-dependent theory, the mTOR/PI3K signaling pathway theory is also important, where mTOR/PI3K functions as the upstream regulator of ribosome biogenesis and plays a key role in protein synthesis (206). The mTOR/PI3K inhibitor GSK2126458 and the RNA polymerase 1 inhibitors CX5461 and BMH21 have been developed, all of which have shown very good therapeutic effects in a mouse model of human EM (206).

In terms of the MIF theory, the study by Khoufache *et al* (207) showed that the specific antagonist of MIF (ISO-1) can effectively reduce the growth and progression of ectopic endometrium, indicating that this agent has good clinical potential (207). The research and development of other associated drugs is still in the experimental stage and requires additional attention.

4. Complement system

Complement system in EM. The complement system is an indispensable part of the innate immune response and is involved in the identification and elimination of pathogens and abnormal cells, such as apoptotic and necrotic cells (208-210). The complement system recognizes and tags pathogens and altered or transformed self-cells, thereby activating the inflammatory response and modulating the adaptive immune response, and ultimately leading to the lysis of target cells or pathogens (211). The complement system is a functionally complex system that can trigger a severe immune response or inflammatory process (211). This system may be harmful to the body when it is excessively or abnormally activated in conditions such as inflammation or tissue damage (212-215). The complement system has a considerable role in peritoneal inflammation, which is associated with the early stages of EM (216).

The complement system is formed from a group of small proteins that demonstrate enzymatic activity after activation and exist in the serum and tissue fluid of healthy individuals and animals. The components of the complement system are extremely complex and variable. The study by Aslan *et al* (217) reported that 23 out of 84 immune response genes were upregulated in patients with EM, two of them considerably so. Some of these differentiating molecules were later confirmed to be members of the complement system (217).

Upregulated members of complement system in patients with EM. In a previous study, most components of the complement system that are associated with EM were found to be upregulated in patients with EM (218). To the best of our knowledge, a limited number of complement components were found to be decreased. Such decreased components included mannose/mannan binding lectin-associated serine protease-1 (MASP-1), and several remain controversial (219).

In a previous study, the quantities of C1q and C1INH in the peritoneal fluid of patients with EM at various stages were considerably increased compared with those in normal controls (220). Moreover, increased levels of C1q and C1INH were found in the peritoneal fluid of early stage EM (220). These results suggest that immunoglobulins participate in

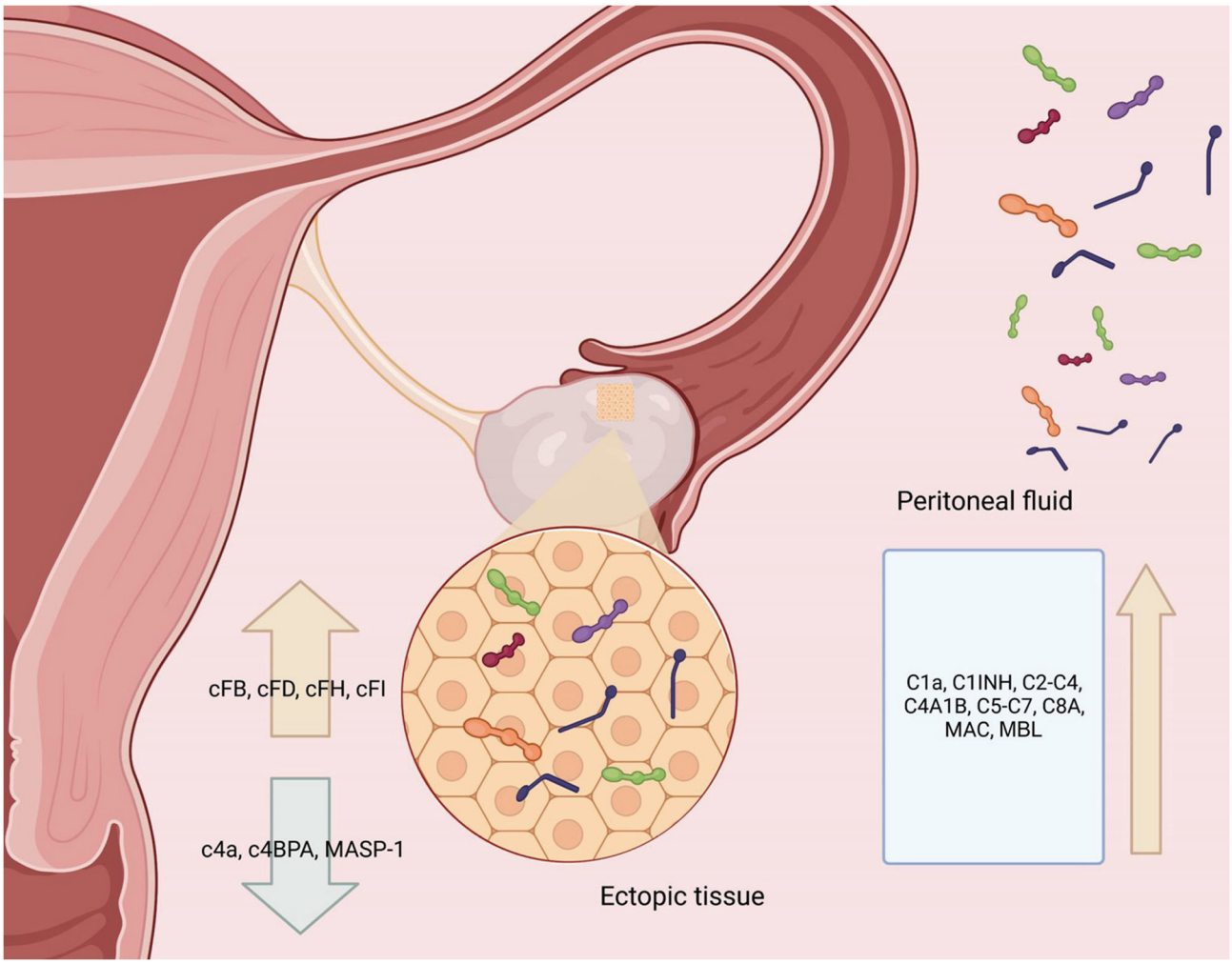

Figure 5. Regulation of the completement system in EM. ↑ and ↓ represent upregulation and downregulation, respectively, in the ectopic tissue and peritoneal fluid of patients with EM. In the ectopic tissue, the upregulated complement components include cFB, cFD, cFH, and cFI, while the downregulated components include c4a, c4BPA and MASP-1. In the peritoneal fluid, C1a, C1INH, C2-C4, C4A1B, C5-C7, C8A, MAC and MBL are all upregulated. cFB, complement factor B; cFD, complement factor D; cFH, complement factor H; cFI, complement factor I; C4BPA, complement component 4 binding protein α; MASP-1, mannose/mannan binding lectin-associated serine protease-1; C1a, activated first component of complement; C1INH, C1-esterase inhibitor; C, complement; MAC, membrane attack complex; MBL, mannose-binding lectin.

the initiation of the classical pathway in ectopic endometrial tissue, especially during early EM (220). Furthermore, C1-associated genes (including C1QA, C1QB, C1R and C1S) and C2 genes were increased in ectopic endometrial tissues compared with those in healthy controls (221). C3 is usually expressed in the ectopic tissue of patients with EM despite its regular expression levels in the glandular epithelium of normal endometrium (222,223). The overall C3 levels in the peritoneal fluid and peripheral blood of patients with EM were increased compared with those of normal controls, especially C3c and C3b (219,224-227).

A growing body of evidence has reported that the C3 levels in the serum of patients with EM were considerably upregulated, in particular among patients with mild EM, when compared with that in healthy subjects and patients with severe EM (228-231). Other studies found that the C3 levels in the eutopic endometrium of patients with EM were also considerably increased under the influence of ectopic endometrial tissue (228,232). Elevated iC3b in the peritoneal fluid of patients with EM may negatively regulate NK cell activity via the iC3b/CR3 signaling pathway, thereby downregulating NK cell cytotoxicity (219,233).

The levels of other members of the complement system, such as C5, C6, C7 and C8A, were also upregulated in the ectopic endometrial tissue of patients with EM (217,221). C6 levels were considerably increased in patients with early stage EM compared with those in their healthy counterparts (234). C7 was also upregulated in ectopic endometrial tissue (221).

The expression levels of complement factor (CF)B, CFD, CFH and CFI in the complement system are upregulated in ectopic EM tissue, while the expression level of MASP-1 is downregulated (Fig. 5).

Controversies. There are controversial theories about the relationship between C4 and EM. Studies have shown that the concentration of C4 in the peripheral blood and peritoneal secretions of women with EM are increased compared with those of normal controls (219,224,225). C4a was considerably decreased in the peritoneal fluid of patients with peritoneal and ovarian EM (218,235). The C4A/B gene expression level

was upregulated in ectopic endometrial tissues, while complement component 4 binding protein α (C4BPA) expression level was reduced (221).

Two studies have examined the membrane attack complex (MAC; also known as SC5b-9) in patients with EM. One study found that the MAC levels in the peritoneal fluid and peripheral blood of patients with EM were increased. The concentrations of terminal complex were also increased in patients with advanced EM (219). However, another study found no considerable difference in the MAC level in the peritoneal fluid in patients with EM compared with that in normal controls (236,237).

The relationship between mannose-binding lectin (MBL) and EM is also controversial. Some studies have shown that equivalent MBL levels exist between normal controls and patients with EM (238,239), while the study by Sikora *et al* (220) observed an increased level of MBL in the peritoneal fluid of patients with EM. Furthermore, the concentration of MBL in patients with early EM was increased compared with that in patients with late EM (218,220,236,237,240).

Potential therapeutic targets associated with the complement system. Complement C3 inhibitors can interrupt the inflammatory cascade at its earliest stage and reduce the production of iC3b, which weakens NK cytotoxicity. The blockade of C5a and C3a to induce macrophage activation, C1q inducing the transformation of macrophages to the M2 phenotype and angiogenesis in EM lesions via complement immune therapy could all be promising targets for EM treatment (241,220).

5. Sex steroid hormones

Sex steroid hormone regulation and immune alteration in EM. Estrogen and progesterone are two key sex hormones that are closely associated with the occurrence and progression of EM. As previously discussed, estrogen mainly exerts its functions by interacting with ER and inducing an inflammatory environment. ER2 is associated with the inhibition of the inflammatory response. Increased ER2 activity can promote cell survival by inhibiting TNF1-mediated apoptosis, participating in growth factor signaling and promoting epithelial mesenchymal transition (242).

The close relationship between sex hormones such as estrogen and progesterone and the immune system has been frequently demonstrated. Estrogen can induce the activation of the immune response and immune cells through nuclear receptors. The dysregulation of estrogen and progesterone signaling in EM are termed estrogen dominance and progesterone resistance (243,244).

The binding of progesterone to progesterone receptor (PR) in epithelial and stromal cells inhibits epithelial cell proliferation and promotes decidualization (245). These effects of progesterone are achieved by the integration of the response through two functionally different subtypes of PR: PR-A and PR-B. These two subtypes share the same gene but have separate promoters, which makes their structure and function distinct from one another (246). PR-A is recognized as the initial driver of uterine PR function, while PR-B is key to progesterone-induced morphogenesis during pregnancy, and mainly improves progesterone reactivity by maintaining an appropriate ratio to PR-A (247).

Estrogen and its two nuclear receptor subtypes have already been briefly introduced in the preceding sections. Estrogen promotion of epithelial cell proliferation and endometrial stromal decidualization is also mediated by the binding of estrogen and its receptors. The two receptor subtypes, ER1 and ER2, are transcribed by different genes (248).

ER1 is expressed in most cells of the immune system, while ER2 is limited to certain cell types of some immune organs, such as lymphocytes in human lymph nodes, bone marrow and thymus. Therefore, ER1 has a stronger impact on the immune system than ER2 (220). Both ER subtypes are expressed in the endometrium, with the expression levels of ER1 outnumbering those of ER2 (249). ER1 also has a more important role in promoting the proliferation of endometrial epithelial cells, implantation and fertilization than ER2 (221). The response induced by estrogen binding to ER1 may be mediated by slower genomic signaling pathways such as the IGF-1-PI3K/AKT pathway (250). As aforementioned, ER2 is associated with the inhibition of the inflammatory response. Increased ER2 activity can promote cell survival by inhibiting TNF1-mediated apoptosis, participating in growth factor signaling and promoting epithelial mesenchymal transition (242).

In addition to the two aforementioned types of sex steroid hormones, the abnormal elevation of prostaglandins (another hormone that induces an inflammatory response) is also involved in the pathophysiological changes of EM. Increased PGE2 is detected in both the eutopic and ectopic endometrial tissues of patients with EM. PGE2 participates in the direct and indirect induction of pain through positive feedback with estradiol (E2). In this positive feedback loop, E2 activates cyclooxygenase II (COX2) to promote the production of PGE2, and the upregulation of PGE2 level in turn promotes the expression of steroidogenesis-associated genes and aromatase, thereby increasing E2 production (251). Sensitivity to IL-1β is important in the regulation of COX2, which contributes to the maintenance of sex hormone-associated inflammation in EM lesions (165).

Endometriotic changes of sex steroid hormone. Abnormal regulation of sex hormone nuclear receptors in patients with EM has been reported (252). The main dysregulations of sex steroid hormones in EM can be classified into two types: Estrogen dominance and progesterone resistance.

Estrogen dominance refers to estrogen-induced cell proliferation and inflammation. The estrogen response is primarily triggered by ER1 and ER2. These two receptors have different behaviors, and thus the expression level and ratio of these two receptors are important to determine effects of estrogen on EM. The ratio of ER1:ER2 is decreased in ectopic endometrial tissue of the ovary. This decreased ratio is caused by the upregulation of ER2 and the downregulation of ER1 due to changes in the methylation level of their promoters (249). Decreased methylation of the ER2 promoter leads to increased expression levels of ER2, while increased methylation of the ER1 promoter leads to decreased ER1 expression levels (251,253). In addition to epigenetic changes, crosstalk between ER1, ER2 and PRs has also been found to be important. ER2 directly downregulates the expression of ER1 by binding to the promotor region of ER1 (254). The downregulation of ER1 contributes to the reduction of PR and further promotes the development of EM and infertility (255).

ER2 upregulation in EM can activate a variety of proliferation- and inflammation-associated signaling pathways, such as the COX2-PGE2 feedback loop, which may be the main reason for increased lesion survival, cell proliferation and inflammation (249). Other research has found that ER2 can interact with inflammatory factors to regulate apoptosis and the inflammatory response, which is also associated with the pathogenesis of EM (172).

The other sex steroid hormone dysregulation in EM is progesterone resistance, in which normal and ectopic endometrial tissues in patients with EM do not respond to progesterone (256). Little is known about the mechanism behind progesterone resistance. Several studies have suggested that the downregulation of progesterone receptors may be a potential contributor to progesterone resistance, but this remains controversial (257,258).

Hormone therapies and therapeutic targets. Studies have shown that the hormonal treatment of EM is feasible (249,259). Current hormone therapies include GnRH agonists, aromatase inhibitors, COCs containing progesterone and E2, progestin-based therapies and androgen therapy (25,260,261). Hormone therapy aims to inhibit lesion growth or control pelvic pain by reducing the estrogen response and promoting the progesterone response (25,262). However, hormone therapy interferes with ovarian function, homeostasis and individual immunity, resulting in numerous side effects that include weight gain, androgen effects, reduced bone density, infertility and other adverse effects (262). Clinically, hormonal therapies are currently the most effective drugs for the treatment of EM (1,260). COCs are generally composed of a specific proportion of estrogens and progestogens that can inhibit steroid production in the ovary to treat chronic pelvic pain caused by ectopic endometrium (263). Although COCs are effective against the post-operative recurrence of EM, the estrogen contained in COCs still carries a risk of aggravating progestin resistance. Progestogen-based hormone therapy is another ideal treatment for EM. Medroxyprogesterone acetate (MPA) has been effective at reducing the pain caused by EM and reversing the decreased bone mineral density caused by low estrogen levels (264). A decrease in ER and an increase in PR in endometrial tissue can be found in patients with EM using MPA and other progestin-based drugs (265,266). GnRH agonists are second-line drugs after hormone therapy, which can reduce the production of estrogen, weaken E2 dominance and downregulate pituitary function through negative feedback (261). Although GnRH agonists are effective at alleviating the pain caused by EM, their side effects, such as bone loss, greatly limit their clinical use. As aforementioned, there are still several obstacles that block the treatment of EM with hormone therapy, including unresponsiveness to progesterone caused by progesterone resistance and the adverse effects of hypoestrogenemia.

6. P-selectin

The inflammatory and coagulation systems are the two main host defense systems. The coagulation system can be triggered by the inflammatory system (267,268). Inflammation is regulated by coagulation. P-selectin is a platelet adhesion molecule, whose expression levels are regulated by protein kinase C. Studies have found that its expression level is abnormal in patients with EM (269-271). The study by Guo *et al* (272) reported that platelet aggregation was induced by P-selectin in ectopic endometrium, which promoted the proliferation and progression of the cell cycle for endometriotic stromal cells (272). Studies have found that P-selectin is also involved in leukocyte adhesion and inflammation (273,274). P-selectin is therefore considered a potential immune-associated therapeutic target. P-selectin can be targeted and blocked in several ways. For example, inclucumab is a highly specific recombinant human monoclonal antibody against P-selectin, and has been in clinical trials for the treatment of myocardial injury (275). The Fc fragment of recombinant P-selectin has also been tested in a mouse model of human EM, where it was effective without signs of bleeding complications (272). However, to the best of our knowledge, there are no reports of the clinical use of P-selectin antagonists or antibodies to treat EM.

7. Future perspectives

The treatment of EM still primarily uses hormone-regulating drugs, such as progesterone-based therapy, GnRH agonists, aromatase and COX inhibitors, and COC. Although clinical trials have shown the effectiveness of hormone therapy, patients still focus on its moderate or severe adverse effects, such as osteoporosis and sexual function inhibition. Studies have tested the effects of various compounds on EM, hoping that these compounds have therapeutic effects on EM without side effects. In the present review, several compounds are discussed that have been shown to be capable of improving symptoms of EM in animal experiments, clinical trials or both. Dienogest is a derivative of 19-nortestosterone, which serves the dual roles of anti-ovulation and anti-proliferation against endometrial cells, which can effectively relieve EM symptoms without the side effects of estrogen and androgens (276). Clinical randomized controlled trials at different stages have been carried out in Europe and Japan, whose results show that Dienogest is superior to other progesterone drugs in terms of efficacy, safety, receptor selectivity and tolerance in the treatment of EM (277,278). Although Dienogest has numerous advantages over other hormone drugs, severe bleeding seems to be a potential serious side effect.

Beyond hormone-associated therapy, researchers are also committed to studying and developing drugs targeting other immune-associated factors to treat of EM. Since the first anti-complement drug eculizumab (anti-C5 antibody) was approved by the US Food and Drug Administration for the treatment of paroxysmal nocturnal hemoglobinuria in 2007, more complement pathway blocking drugs have been fully developed (279).

In addition to studying drugs targeting immune system factors, researchers are also studying the utility of ribosome biosynthesis (associated with macrophage proliferation) in the treatment of EM. Chang *et al* (206) tested the potential of using ribosome biogenesis inhibitors targeting mTOR/PI3K and RNA polymerase I as an alternative to the treatment of EM in an animal study in 2022. The results showed that the ribosome biogenesis inhibitor could inhibit inflammation,

reduce neutrophils in the peritoneal fluid and relieve pain in the treatment of an EM mouse model, which confirmed its therapeutic potential (206).

In previous decades, there has been a push towards efforts to find other potential targets for the treatment of EM. It has become a consensus that local and systemic changes to immune cells and immune-associated factors are important to the pathogenesis and development of EM. More attention should be paid to the development of drugs that target the components of the immune system. To the best of our knowledge, numerous side effects can be avoided by immunotherapy, which should be the direction of future research on EM treatment. Immunotherapy targeting NK cells and macrophages is in the preclinical trial stage, which may inspire other researchers to seek improved immune-associated solutions.

8. Conclusion

Ectopic endometrial tissue in patients with EM is a clone of ectopic proliferating endometrial cells in the immune microenvironment of the inflammatory response, which is characterized by increased estrogen pro-inflammatory cytokine levels and alterations to the immune cell infiltration spectrum. The pathogenesis of EM remains unclear, and it is relatively difficult to find and select a satisfactory treatment for this disease. To the best of our knowledge, there is no treatment plan that can completely cure EM. At present, the treatment of EM is mainly symptomatic, and includes reducing pain, avoiding infertility and delaying recurrence as much as possible. Compared with the inefficiency of medical symptomatic treatment, laparoscopic surgery is still the first choice for patients with EM of childbearing age due to its high postoperative pregnancy rate. However, as with all surgeries, conservative surgery in patients with EM may only require partial ovariectomy. Hysterectomy is occasionally required, but there is a risk of over-operation or premature ovarian failure. Hormone therapy for EM is not ideal and is usually accompanied by side effects. Thus, although there are limited studies on the clinical application and evaluation of immune targeted therapy and personalized therapy for EM, it is still necessary to further investigate this area.

The present review discussed the role of five major factors (NK cells, macrophages, the complement system, sex steroid hormones and P-selectin), and summarized their functions, regulation and association with EM. Several potential therapeutic targets for EM have also been summarized, whether they are in the hypothetical stage or established by animal experiments. It is hoped that through the present review, more attention can be given to EM and its potential therapeutic targets, further advancing EM treatment methods.

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Availability of data and materials

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Author's contributions

WZ, KL and XZ designed the research, WZ and KL collected and analyzed the reference articles, and wrote the draft. GZ and AJ designed the figures, XZ and GZ critically revised the manuscript. All authors contributed to manuscript revision, and read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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