COMMENTARY

Role of neutrophils in the immune microenvironment of endometriosis

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Abstract

Endometriosis (EMs) is a common systemic estrogen-dependent chronic inflammatory disease in gynaecology. Available evidence indicates that immune factors exert extremely important functions in the pathogenesis of EMs. As a key cell group in the immune environment, neutrophils have been found to be implicated in EMs progression in various studies. In this paper, the function and mechanism of neutrophils in the immune microenvironment of EMs are summarized, providing new research ideas for the etiology and pathogenesis of EMs. *(Afr J Reprod Health 2025; 29 [5s]: 13-19).*

Keywords: Endometriosis; Immune microenvironment; Neutrophils; Pathogenesis

Résumé

L'endométriose (EM) est une maladie inflammatoire chronique systémique œstrogéno-dépendante fréquente en gynécologie. Les données disponibles indiquent que les facteurs immunitaires jouent un rôle crucial dans la pathogenèse de l'EM. En tant que groupe cellulaire clé de l'environnement immunitaire, les neutrophiles sont impliqués dans la progression de l'EM dans diverses études. Cet article résume la fonction et le mécanisme des neutrophiles dans le microenvironnement immunitaire de l'EM, offrant ainsi de nouvelles pistes de recherche pour l'étiologie et la pathogenèse de l'EM.. *(Afr J Reprod Health 2024; 29 [5s]: 13-19).*

Mots-clés: Endométriose ; Microenvironnement immunitaire ; Neutrophiles ; Pathogénèse

Introduction

Endometriosis (EMs) is a common systemic, estrogen-dependent chronic inflammatory disease in gynaecology, which refers to the appearance and growth of endometrial tissue (glands and interstitium) outside the uterus, resulting in pain, infertility, as well as pelvis masses.[1] In recent years, about 10% of women of childbearing age have been reported to suffer from EMs, which seriously influences women's quality of life and social wellbeing.[2] Since non-invasive diagnostic markers of EMs are lacking and there is no known cure for EMs, it is important to explore the factors that promote the survival, infiltration, and vascularization of EMs lesions.[3] Available studies indicate that immune factors have crucial roles in EMs pathogenesis.[4]

In recent years, more attention have been paid to the role of neutrophils in the study of EMs.[5] Neutrophils are present in large numbers in all immune cells, are continuously produced, are highly cytotoxic, and produce extracellular traps, which lay the foundation for their ability to have effective protection in infectious diseases.[6] However, recent studies have shown that neutrophils have functions beyond their role in fighting infections.[7] Studies have shown that compared with neutrophils of healthy control subjects, systemic circulating neutrophils of EMs patients have a unique transcriptome profile, and in immunoactive mouse models, neutrophils are quickly recruited into the peritoneal environment early after establishing EMs lesions and persist in mouse lesions for long periods of time.[8] Besides, in vivo neutrophil reduction alters EMs mice's systemic and peritoneal immune microenvironment, highlighting a new role of neutrophils in the early stage of EMs. The function of neutrophils seems to be regulated by the local

microenvironment, which is related to the regulation of angiogenesis and local inflammatory environment associated with EMs pathogenesis, and may exert a crucial role in early diagnosis and treating of EMs, which is particularly important for the study of the efficacy and prognosis of EMs.[9] In this paper, the highly complex and dynamic mechanisms of immune microenvironment such as inflammation and angiogenesis mediated by immune cell population interaction in the pathogenesis of EMs are summarized, and the functions and mechanisms of neutrophils in the immune microenvironment of EMs are explored, which provide new research ideas for the exploration of the etiology and pathogenesis of EMs.

Relevant immune cell populations in the EMs immune microenvironment

Neutrophils, macrophages, natural killer (NK) cells, T lymphocytes as well as dendritic cells (DCs) are mostly implicated in the pathophysiology of EMs in the innate immune system.[10] We briefly explain the role of these immune cells and neutrophils in EMs pathogenesis.

Macrophage is an important cell type in the innate immune system, which has key impacts on the body's defense, inflammatory response, as well as immune regulation.[11] Studies have shown that the density of macrophages in the abdominal cavity of EMs is increased, and the inflammatory phenotype of endometrial macrophages is increased, while the phagocytosis capacity is decreased.[12] The expression of tumor necrosis factor (TNF-α), interleukin (IL)-6 along with IL-1β expression in macrophages of EMs peritoneal fluid is significantly increased, which facilitates ectopic endometrial stromal cells (eESCs) proliferation and invasion, leading to endometrial lesions. These pro-inflammatory cytokines exert a function in subsequent neutrophil recruitment process.[13] In addition, overexpression of estrogen and progesterone resistance result in dysfunction of the abdominal immune microenvironment, increased estrogen receptor α (ERα) along with estrogen receptor β (ERβ) expression, induced polarization of macrophages recruitment and replacement of activated macrophages (M2 type), reduced phagocytosis and pro-inflammatory cytokine expression, inhibited inflammatory response, and changed the local immune microenvironment, which promote the formation of EMs lesions.[14] These evidences suggest that macrophages help ectopic endometrium evade immune surveillance in EMs, and the pro-inflammatory cytokines expressed by macrophages can regulate neutrophil recruitment and promote the occurrence and development of disease.[15]

NK cells belong to cytotoxic effector lymphocytes in human body, which have anti-tumor, anti-viral infection and immunomodulatory functions.[16] NK cells in the abdominal cavity of EMs does not only decrease cytotoxicity, but also significantly reduces chemotaxis.[17,18] The reduction of NK cytotoxicity may be influenced by transforming growth factor-β (TGF-β), IL-6 as well as IL-15 in the abdominal cavity, which are also closely related to the cytokines produced by neutrophils.[19] The immune escape of ectopic endometrium fragments in the abdominal cavity makes it easier for ectopic endometrium to survive in the abdominal cavity, and finally promotes EMs progression.[20] In addition, estrogen represses cytotoxic activity of NK cells due to low autophagy of eESCs, facilitating ESCs immune escape as well as pathological development.[21] Therefore, cytokines produced by neutrophils are associated with reduced chemotaxis and activity of NK cells, which can promote EMs progression.[22]

T lymphocytes are human cellular immune response cells, they not only participate in cellular immune response, but also have a vital role in regulating the body's immune response.[23] Among them, the important members of the $CD4^+$ (helper T lymphocyte) subgroup of T lymphocytes can be divided into Th1, Th2, Th17 as well as regulatory T cells (Treg cells).[24] Peritoneal fluid in EMs patients has immunoregulatory and immunosuppressive effects, shifting Th1/Th2 cytokine balance to Th2 response, leading to local immunosuppression and promoting implantation of ectopic endometrium.[25] Studies have found that neutrophils cultured in the supernatant of ovarian endometrial cysts can inhibit the proliferation and activity of autologous T cells.[26] In addition, Th17 cells can rapidly initiate inflammatory response through the recruitment, activation, and migration of neutrophils, leading to increased inflammation and promoting the

proliferation of eESCs.[27] $CD4^+$T cells have high expression of IL-27 receptor, and IL-27 promotes IL-10 production by Th17 cells and promotes the rapid proliferation and invasion of ectopic lesions[27]. Elevated Treg levels are found in EMs patients' peritoneal fluid, accompanied by over-activation of ERα, which trigger the expansion of Tregs as well as the secretion of cytokines (IL-10 and TGF-β1), enhancing the aggressiveness and cellular activity of eESCs.[28] Additionally, IL-8 levels are increased in the peritoneal fluid of EMs due to autophagy defects in EMs patients, and IL-8 may induce T lymphocyte apoptosis by increasing apoptosis-related factor ligand (FasL), providing a local immune tolerance environment and reducing the apoptosis rate of ectopic ESCs.[25,28] These studies have shown that the characteristics of T lymphocyte subpopulations in EMs patients are altered and can rapidly initiate inflammatory responses through neutrophils recruitment, activation, and migration, promote their immunosuppression, leading to the survival, growth, and invasion of eESCs, and participating in the pathophysiology of EMs.[29]

Dendritic cell (DC) is a major antigen-presenting cell specialized for antigen initiation and modulation of adaptive immune responses.[30] Recent studies have found that increased abdominal DC density in EMs patients, especially in the early stage of EMs, promotes the onset of EMs, and the maturation of abdominal DC also has a key role in EMs development.[31] After treatment with lipopolysaccharide, the proportion of mature DC increases significantly, which can reduce the volume and weight of EMs lesions.[32] Peritoneal DC in EMs tissues has high expression of mannose-receptor and can phagocytizedead eESCs fragments, but may promote the inflammatory state of patients by secreting IL-6 and IL-1β, and may also promote neutrophil recruitment.[33] In addition, it has been documented that plasma cell-like DC enhances endothelial cell migration by secreting IL-10, promotes angiogenesis and pathological growth of EMs tissue.[34]

Neutrophils in the abdominal immune microenvironment and Ems

Neutrophils, as a kind of cell with a large proportion in the white blood cells, have a crucial impact on the human immune system, especially in the immune microenvironment.[35] Neutrophils play a number of key roles in the immune microenvironment, including anti-infection defense, tissue repair and regeneration, removal of necrotic tissue and foreign substances, promotion of inflammatory processes, and maintenance of microvascular permeability.[36]

Symons *et al*. showed that neutrophils were rapidly recruited into the abdominal environment early after the establishment of EMs lesions, and remained in the lesions of mice for a long time, showing alterations in pro-inflammatory and angiogenic mediums.[8] These findings highlight the crucial role of neutrophils in early events of EMs, containing angiogenesis and regulating the local inflammatory environment linked to EMs pathogenesis.[37] In the early stage of EMs development, neutrophils infiltrate the abdominal cavity and EMs tissues and secrete angiogenic factors and cytokines, suggesting that neutrophils have a vital role in the early stage of EMs development.[38] Neutrophil aggregation may be because of elevated concentrations of chemokines containing IL-8, epithelial neutrophil activating peptide 78 (ENA-78), as well as human neutrophil activating peptide (HNP1-3) in EMs patients' plasma and peritoneal fluid.[39,40] Among them, ENA-78 is a neutrophil chemokine, which not only stimulates neutrophil secretion of growth factors and cytokines, but also promotes neovasculation of EMs.[41] The levels of HNP1-3 in EMs patients' peritoneal fluid are significantly increased, which is closely related to the concentrations of neutrophils, T cells and IL-8 along with the severity of the disease, indicating that HNP1-3 and neutrophils are worthy of evaluation as targets for anti-EMS therapy.[42] An in vitro experimental study has found that adding IL-1β or TNF-α to ESCs can promote the release of ENA-78, IL-6 as well as IL-8, which can cause neutrophils to accumulate.[43] In addition, neutrophils can also produce angiogenic factors containing VEGF and pro-inflammatory cytokines containing IL-8, reactive oxygen species, as well as activated matrix metalloproteinase (MMP)-9, causing angiogenesis and promote the progression of EMs.[44] Some studies have indicated the potential therapeutic benefits of tumor necrosis factor-associated apoptosis-inducing ligand (TRAIL) on

neutrophilic inflammation.[45] Reduced expression level of TRAIL is conducive to neutrophilic survival and promotes angiogenesis, indicating the potential therapeutic benefits of TRAIL in neutrophilic inflammation.[46]

Neutrophil extracellular traps (NETs) are reticular chromatin structures that are involved in the pathogenesis of immune-linked diseases.[47] The ability of early NETs to clear pathogens has aroused much enthusiasm, but their pathogenic potential has attracted more recent attention, including their involvement in aseptic inflammation and disease pathology.[48] The study of Berkes *et al*. showed that the number of NETs in EMs patients' peritoneal fluid was significantly increased compared with non-EMs control group, and NETs may be involved in the pathophysiological process of EMs, which needs to be confirmed by further studies.[49] In addition, recent studies on breast degeneration have shown that estrogen function supports neutrophil infiltration as well as the establishment of a neutrophil mediated tumor-promoting microenvironment.[50] Thus, EMs is built in a highly complex and dynamic intraperitoneal microenvironment of inflammation and angiogenesis modulated by neutrophils as well as other immune cells.[51]

In EMs patients, there are differences in the presence of endometrial immunoinflammatory genes, especially genes involved in the regulation of apoptosis and decellularity that affect neutrophil recruitment and function.[52] In the EMs mouse model, neutrophils are rapidly recruited into the abdominal environment early after the establishment of EMs lesions and persisted in the mouse lesions for a long time, implying that neutrophils play a key role in the early development of lesions[8]. Another study designed glucose oxidase-supported bovine serum albumin nanoparticles (BSA-GOx-NPs) and found that neutrophils were continuously recruited to ectopic lesions in EMs, specifically delivered to ectopic lesions in a neutrophil-dependent manner, consumed glucose and induced apoptosis in ectopic lesions.[53] For the first time, the neutrophil hitchhiker strategy has been shown to be effective in chronic inflammatory diseases and provides a non-hormonal and easily achievable approach for the treatment of EMs.[53] In addition, hormones activate neutrophil function in multiple ways.

An animal study found that inhibiting estrogen signaling pathway could reduce the number of neutrophils along with the expression of pro-inflammatory cytokines, thereby inhibiting the growth of EMs lesions.[54] In addition, studies have shown that IL-17A produced by neutrophils plays an important role in promoting peritoneal angiogenesis and pro-inflammatory environment to establish and maintain EMs lesions,[55] and IL-17A triggers the production of growth-regulating oncogene-α (GRO-α) by EMs interstitial cells, thus recruiting more neutrophils and inducing persistent inflammation in EMs.[56] IL-8 is a powerful angiogenic cytokine that induces neutrophil chemotaxis, further accelerating disease progression in EMs.[57] The increase of neutrophils is related to the etiology of EMs, inducing a vicious cycle of endometrial cell adhesion, proliferation and further secretion of related inflammatory cytokines.[58]

Clinical application of neutrophils in EMS

It has been confirmed that neutrophil to lymphocyte ratio (NLR) combined with serum CA-125.59 can participate in EMs diagnosis and improve diagnostic accuracy.[59] In addition, studies have found that preoperative NLR levels have a high predictive ability for postoperative fertility in ovarian EMS infertile patients.[60] The association between NLR and chronic pelvic pain can provide clinicians with further tips to develop specific treatment methods and follow-up plans related to various expressions of NLR.[9] Early diagnosis and evaluation of the disease, as well as early treatment are particularly important for the efficacy and prognosis of patients, which can provide a new non-interventional, non-invasive examination for EMs diagnosis, and can also be used as the latest therapeutic target of EMs.[61]

Conclusion

We discuss how EMs lesions are built in a highly complex and dynamic intraperitoneal microenvironment of inflammation and angiogenesis modulated by neutrophils along with

other immune cells. We find that ectopic endometrial lesions lead to rapid recruitment of neutrophils, and neutrophil infiltration promotes positive feedback in the early angiogenic inflammatory microenvironment of ectopic endometrial. In addition, angiogenesis is a necessary condition for ectopic lesion implantation and cell proliferation, in which angiogenesis related factors play an important role, which is also one of the important mechanisms of the occurrence and development of EMs. A variety of angiogenesis inhibitor drugs have been regarded as potential EMs treatment options.

Competing interests

The authors report no actual or potential conflicts of interest.

Contribution of authors

Zhang JH and Mei SS: conceived and designed the study, collected and analysed the data. Zhang JH and Wang XY: prepared the manuscript. All authors mentioned in the article approved the manuscript.

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