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Immunology of endometriosis

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A B S T R A C T

The pathophysiology of endometriosis is not completely understood, but an aberrant immune response in the peritoneal environment seems to be crucial for the proliferation of ectopic endometrial cells – as those cells escape apoptosis and peritoneal cavity immunosurveillance. The growth of endometrial implants leads to the recruitment of a large number and diversity of immune cells and intense inflammation with increased pro-inflammatory cytokines, growth factors, and angiogenesis. There is substantial evidence of aberrant function of almost all types of immune cells in women with endometriosis: decreased T cell reactivity and NK cytotoxicity, polyclonal activation of B cells and increased antibody production, increased number and activation of peritoneal macrophages, and changes in inflammatory mediators. New clinical treatments for endometriosis are an urgent need, especially nonhormonal drugs. The study of immunology may

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clarify its role in the pathogenesis of endometriosis and contribute to the development of new therapeutic strategies.

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Endometriosis is a hormono-dependent inflammatory gynecological disease whose pathophysiology is not completely understood. A peritoneal environment that allows the proliferation of ectopic endometrial cells associated with an aberrant immune response seems to contribute to the development of the disease. Although several immunological abnormalities have already been reported, the role of the immune system in endometriosis is not well established [1].

Disturbances in immune homeostasis are associated with increase in implantation, proliferation, and angiogenesis of the ectopic endometrial tissue [2]. However, it is not clear whether the modifications of the immune response lead to the development of the disease or if they are consequences of the ectopic endometrial growth [3].

The study of immunological dysfunctions in the context of endometriosis may help in understanding its role in the pathogenesis of the disease and could contribute to the development of new therapeutic strategies in the future.

Immunosurveillance: importance of immunological disorders in the survival and proliferation of ectopic endometrial cells

One of the main theories of the pathogenesis of endometriosis is the retrograde menstruation – the dissemination of endometrial cells through the uterine tubes – first described by Sampson (1927) [4]. However, it is known that this phenomenon occurs in most women of reproductive age, but not all of them develop the disease. Once they reach the peritoneal cavity, the endometrial cells in healthy women do not implant and are eliminated by an “immunosurveillance” system through apoptosis [3].

It was proposed that, in women with endometriosis, changes in cell-mediated and humoral immunity may contribute to the development of the disease [5]. These changes probably prevent the clearance of the endometrial cells that reach the peritoneal cavity and allow their implantation and development [3].

The exact mechanisms of immunosurveillance evasion by ectopic endometrial cells remain unclear, and some hypotheses have been formulated to explain this phenomenon. The production of proteins by the implants – such as the soluble form of the ICAM (intercellular adhesion molecule)-1, the sICAM-1 – could interfere in their recognition by the leukocytes. It has been described that the expression of ICAM-1 mRNA and the secretion of sICAM-1 are increased in endometriotic stromal cells compared to those in stromal cells from eutopic endometrium. The circulating sICAM-1 binds to leukocyte function antigen-1 (LFA-1) and makes leukocytes less available to recognize the aberrant endometrial cells through their cell surface ICAM-1 [6].

Dysfunctional cells are eliminated by apoptosis in the normal endometrium as part of a tissue repair mechanism during each menstrual cycle. This normal mechanism of programmed cell death does not occur in ectopic endometrial cells that reach the peritoneal cavity. The overexpression of antiapoptotic factors and decreased expression of proapoptotic factors [7] may interfere in peritoneal homeostasis and contribute to the development of the disease.

The Fas-FasL and TNF-α apoptosis pathways seem to play a key role in the immunosurveillance of the peritoneal microenvironment [8]. It was shown that the peritoneal environment in endometriosis induces FasL expression in stromal cells, leading to a Fas-mediated apoptosis of activated immune cells that express Fas (T cells and NK cells), as a mechanism of immunosurveillance escape [9]. The regulation of apoptosis can be a target for the treatment of endometriosis. It has been shown that the use of GnRH analogs increases the expression of the proapoptotic protein Bax and decreases the expression of the antiapoptotic protein Bcl-2 [10].

It has been suggested that endometrial stromal cells are involved in cellular adhesion to the intraperitoneal surface, whereas glandular epithelial cells play a role in invasion and growth of the lesion [11]. Anomalous expressions of various matrix metalloproteinases seem to be responsible for an

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increased proteolytic capacity in endometriosis [11]. Genetic polymorphisms of matrix metalloproteinase were associated with disease progression, as the combined polymorphisms of genes 12 and 13 seem to protect from deep infiltrating endometriosis [12].

The growth of the ectopic endometrial implants leads to the recruitment of immune cells and an intense inflammatory response, with increased proinflammatory cytokines, growth factors, and angiogenesis. In addition, a mechanism of mobilization of fibroblasts and proliferation of connective tissue is activated to attempt to heal the injury [3].

Endometriosis is a chronic inflammatory disease, and inflammation plays a key role through mitogen-activated protein kinase (MAPK) signaling pathways [13]. Increased cyclooxygenase-2 (COX-2), interleukins, and oxidative stress act through the MAPK pathways [13]. MAPK are dysregulated in endometriotic lesions, and it was shown that their inhibitors can control the disease progression both in vitro and in animal models [14]. However, the use of MAPK inhibitors in the treatment of endometriosis is still limited owing to their teratogenicity and specific adverse side effects [13].

The MAPK pathway can increase inflammation and endometriosis clinic repercussion by recruitment of immune cells and amplification of the inflammatory response [15], generation of an anti-apoptotic signal [16], increased growth factor expression leading to angiogenesis [17], playing a role in the development of pain and hypersensitivity to pain [18] or acting as intracellular and extracellular signal transducers in endometriotic cells [13].

Functional changes in the immunological components of the peritoneal fluid of women with endometriosis have been described, such as in monocytes/macrophages, natural killer (NK) cells, T lymphocytes, B cells, and cytokines [19]. However, the role of these alterations in the development of the disease has not been clarified [20].

Innate immunity: the role of macrophages and NK cells

Macrophages

In the peritoneal fluid, macrophages are the most prevalent type of immune cells [19], and their number and activation are increased in endometriosis [21], as well as their production of cytokines [22,23].

The activated macrophages can regulate the peritoneal environment by phagocytosis that removes red blood cells, damaged tissue fragments, and cellular debris [22] or by the production of soluble mediators like cytokines, prostaglandins, complement components, and enzymes. Through the secretion of these immune mediators, the macrophages can induce inflammation, tissue repair, and neovascularization and may favor the recruitment of fibroblasts and endothelial cells [21,24]. The macrophage-derived cytokines stimulate the activation of other immune cells such as T and B lymphocytes.

Despite the increased activation, the phagocytic activity of the macrophages is reduced in endometriosis [22], as they fail to eliminate the ectopic endometrial cells that reach the cavity through retrograde menstruation. The phagocytosis is regulated through expression of CD36 receptor and activation of matrix metalloproteinases, and both mechanisms are suppressed by prostaglandin E2, which are overexpressed in patients with endometriosis [25].

The scavenger function of the peritoneal macrophages depends on their attachment to extracellular matrix components. Increased nonadherent macrophages have been described in the peritoneal fluid of women with endometriosis, suggesting a defective scavenger function that could lead to the survival of ectopic endometrial cells [23].

In addition to the reduction of phagocytosis ability of macrophages, the amount of regurgitated endometrial cells in the peritoneal cavity may be higher than the capacity of the macrophages to remove them. This factor could contribute to the adhesion and proliferation of these cells and development of the disease [2].

Macrophages exhibit a phenotypic plasticity in their various microenvironments and are classified as two main groups, with different functions [26]: The M1 macrophages, which produce high quantities of inflammatory cytokines and are specialized in the elimination of microorganisms and defective cells, and the M2 macrophages, which modulate adaptive immune response, promote angiogenesis and tissue repair, and scavenge cellular debris.

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An imbalance in M1 macrophages was shown in the eutopic endometrium of women with endometriosis [27]. However, M2 $CD163^{+}$/$CD206^{+}$ macrophages are significantly upregulated in the peritoneum and lesions of women [28] and rhesus macaques with the disease [29]. Experiments with macrophage depletion further demonstrated the key role of M2 macrophages in endometriotic grafting, development, and persistence [28,30]. In addition, selective adoptive transfer of M2 macrophages indicated that they promote endometriosis progression [28].

A recent study [31] evaluated the imbalance in macrophage subtypes in a murine model of endometriosis, considering the classification in large peritoneal macrophages (LPMs) and small peritoneal macrophages (SPMs). The authors have shown an increased proportion of SPMs and an opposite trend for the LPMs. They proposed that this new classification of macrophages should be included in further studies in endometriosis field.

To summarize, the macrophages play a key role in the development of endometriosis once they fail to eliminate the ectopic endometrial cells that reach the peritoneal cavity by retrograde menstruation. In addition, production of inflammatory mediators by macrophages contributes to the implantation and proliferation of endometrial cells, resulting in the development of endometriotic lesions [32].

NK cells

NK cells are lymphocytes of the innate immune system that can kill an array of target cells and secrete cytokines that participate in the shaping of the adaptive immune response and tissue repair. A feature of NK cells resides in their capacity to distinguish stressed cells that have undergone some degree of injuries from normal cells.

The NK cell detection system includes a variety of cell surface activating (KAR) and inhibitory (KIR) receptors, the engagement of which regulates NK cell activities. Among the cell surface activating receptors, two main receptors can be distinguished: NKG2D and CD16 (FcγRIIIa). The latter has the ability to bind and destroy immunoglobulin G (IgG)-coated stressed cells by a mechanism called antibody-dependent cell-mediated cytotoxicity. In addition, the cytotoxic activity of the NK cells can be increased by cytokines such as interleukin-2 (IL-2) [3].

Ectopic endometrial cells that reach the peritoneal cavity achieve to escape the clearance and are not targeted or removed by NK cells in a not completely understood mechanism called “immunoescaping” [8].

A decreased NK cell cytotoxic activity against endometrial cells in women with endometriosis was first described by Oosterlynck et al. (1991) [33] and has been well established since then [34], and it is correlated to the advanced stages of the disease [35]. It is more evident for NK cells from the peritoneal cavity [35,36], of women with endometriosis but is also observed for NK cells in the peripheral blood [35].

Despite the decreased NK cell function in endometriosis, the mechanisms of this suppression are not clear. There is also no consensus regarding the percentage or number of NK cells in endometriosis both in the blood and in the peritoneal cavity [33,37]. Qualitatively, an increased expression of KIR on peritoneal NK cells from women with endometriosis was reported, which could explain the decreased peritoneal NK cell activity in these patients [38].

A decreased cytotoxic function of NK cells could explain the immunoescaping mechanism of endometrial cells, leading to their adhesion and proliferation and resulting in endometriotic lesions. However, it is also possible that this aberrant NK cell function is a consequence of the chronic inflammatory environment provided by the disease [39,40].

González-Foruria et al. (2015) [41] evaluated ligands for NKG2D (a NK cell receptor that triggers a cytotoxic response that activates NK cells) in the peritoneal fluid of women with endometriosis. The authors demonstrated a significant increase in soluble NKG2D ligands, which means a lower expression of these ligands in ectopic endometrial cell surface, and as these soluble NKG2D ligands act as decoy receptors heading toward greater evasion from NK cell recognition.

Macrophage-derived factors such as prostaglandins and cytokines produced in this environment may also modulate NK activity. This hypothesis is corroborated by studies showing the suppression of NK cytotoxic activities by serum and peritoneal fluids of women with endometriosis compared to fluids from control patients [35].

It has been shown that NK cells are important for the interface between innate and adaptive immune response and that they have different subtypes. The NK T cells represent 15–20% of these cells

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and express T-cell receptor (TCR)—CD3 membrane complex, in addition to classical CD 16 expression. They can both kill target cells and secrete cytokines such as IL-4 and IL-10 — which are important in the control of autoimmunity [42].

NK cells contribute to the balance of immune self-tolerance by targeting cells that present self-antigens. Therefore, their reduced activity in endometriosis could explain the increased autoimmune reactivity observed in the disease [2].

Adaptive immunity: T and B lymphocytes

Cell-mediated immunity: T lymphocytes

The B and T lymphocytes are essential subsets for adaptive immunity, which play an essential role in the survival and proliferation of endometrial cells. Indeed, endometriosis is characterized by the reduced activity of cytotoxic T cells, the modulation of cytokine secretion by T helper cells, and autoantibody production by B lymphocytes [22,43].

T lymphocytes are derived from stem cells in the bone marrow and in the fetal liver, and they migrate to the thymus to complete their development. They are classified as several subtypes. The two main groups are those that express the glycoproteins CD4 and CD8, which function as co-receptors for MHC class II and class I molecules, respectively [3,44].

The CD4 T cells can be classified in Th1 and Th2, with different functions: Th1 cells promote the differentiation of the CD8 cells and facilitate cell-mediated immunity by activating monocytes and macrophages; Th2 cells lead to the differentiation of B cells into plasma cells that secrete antibodies. The CD8 T cells can activate macrophages and kill cells that are infected by virus or intracellular pathogens [3,44]. The two groups of lymphocytes secrete different cytokines: Th1: IL-2, IL-12, interferon (IFN)-γ, tumor necrosis factor (TNF)-α and TNF-β; Th2: IL-4, IL-5, IL-6, IL-10, and IL-13 [20].

Studies that have evaluated T lymphocytes in patients with endometriosis showed higher CD4/CD8 ratio and increased concentration of each subset in the peritoneal fluid of the patients, but with a relative reduction in Th1 cells [36]. The endometriotic lesions showed higher concentration of T lymphocytes when compared to that in the eutopic endometrium, but with a similar CD4/CD8 ratio. There were no changes in the peripheral blood [3,44]. Endometriotic lesions also showed higher Th17 lymphocyte fraction when compared to eutopic endometrium [45].

The mechanism of implantation of the ectopic endometrial cells in the peritoneal cavity depends on altered macrophages. These cells also produce inflammatory cytokines that recruit and activate Th1 and Th2 T cells [36].

Another important subset of the T lymphocytes is the regulatory T cells (Treg). They are potent suppressors of inflammatory immune responses and are responsible for maintaining antigen-specific T-cell tolerance and immune homeostasis. A recent systematic review [46] evaluated the role of Treg in endometriosis. The authors concluded that in the peritoneal fluid and in the endometriotic lesions of women with endometriosis, there is a higher concentration of Treg cells and/or their expression markers, when compared with those in controls. However, there is no consensus about the concentration of Treg cells in the eutopic endometrium and peripheral blood of these patients.

Humoral immunity: B lymphocytes and antibodies

Even though immunosurveillance seems to have a defect in endometriosis, some aspects of the immune system are upregulated, such as the widespread polyclonal activation of B cells [47]. B lymphocytes produce antibodies against antigens, and they seem to contribute to the pathogenesis of endometriosis through secretion of autoantibodies [48].

Startseva (1980) [44] first described an increased reactivity of B cells in endometriosis. The same year, another study demonstrated IgG and complement deposits in the endometrium and decreased serum complement, suggesting an autoimmune response with complement consumption by the antigen-antibody complex in patients with endometriosis [49].

A few years later, the presence of antiendometrial antibodies in the serum of women with endometriosis was described [50]. Immunohistochemistry demonstrated that these antibodies could bind

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to topic and ectopic endometrial tissues [51]. Bohler et al. (2007) [52] evaluated the presence and reactivity of IgG in the serum of women with endometriosis against antigens (derived from the membrane, nucleus, and cytosol) from endometrial and ovarian cells. There was a significantly higher level of autoantibodies in patients with endometriosis, when compared to that in controls, and the intensity of the reaction increased with disease progression.

Chishima et al. (2000) [53] proposed possible common alterations between endometriosis and autoimmune diseases: increased B-1 B cells in the peritoneal fluid and B cell production of ANA in the serum of women with endometriosis. However, despite the similarities, it is not possible to consider endometriosis as an autoimmune disease yet. Even if there is a genetic component in endometriosis, a specific association with HLA alleles has not been demonstrated so far [54], nor the specific activation of complement in the endometrium of women with endometriosis [55].

Moreover, polyclonal B cell activation, B-1 cell proliferation, and autoantibodies production may be associated with infertility in these patients [53]. An increased number of B lymphocytes was also observed in the follicular fluid of infertile patients with endometriosis, and it was suggested that this could contribute to endometriosis-related infertility [56].

Some authors have described increased B cells in patients with endometriosis with an inversed correlation with the severity of the disease, suggesting that mild endometriosis (Stages I and II) may be immunologically more active than severe endometriosis (Stages III and IV) [57].

High levels of cytokines that activate B cells were observed in endometriotic lesions, such as BLyS (B lymphocyte stimulator) [58]. This molecule is produced by macrophages and stimulates the development and differentiation of B lymphocytes into plasma cells [59]. Increased BLyS was also described in patients with autoimmune diseases and could be a target for therapeutic strategies for diseases with B cell defects [60]. Interestingly, heterozygosity for the BLyS 817C/T polymorphism was associated with reduced risk of deep infiltrating endometriosis [61].

A recent review [62] evaluated 22 studies concerning the role of B lymphocytes in endometriosis, and almost all of them reported increased number and activation and/or production of antibodies by B cells. It seems that B cells play a role in the pathogenesis of endometriosis; however, further studies are necessary to better understand this association.

Inflammatory mediators: cytokines, chemokines, and growth factors

Increased soluble factors such as autoantibodies, cytokines, growth factors, adhesion molecules, enzymes, hormones, prostaglandins, and reactive oxygen species [16,21,63–66], have been described in the blood, peritoneal fluid, and lesions of patients with endometriosis. This fact is probably a consequence of the high number of leukocytes, macrophages, and other immune cells in the peritoneal cavity of these patients.

These proteins work as mediators of the immune system [67], regulating the proliferation and the differentiation of immune cells, the release of enzymes and acute phase proteins, immunoglobulin secretion, and the cytotoxic activities of immune cells [20].

Studies have shown that the higher concentration of inflammatory mediators in the peritoneal fluid in endometriosis has toxic effects on oocyte pick up by the fimbria, sperm–oocyte interaction, and embryo implantation, leading to an aberrant reproductive function in these women. These effects were reversed during hormonal treatment [3].

Many cytokines – IL-1 [68,69], IL-4 [70], IL-6 [71], IL-8 [72,73], IL-10 [36], IL-33 [74], and TNFα [75] – and growth factors – transforming growth factor (TGF-β) [71], insulin-like growth factor (IGF-1) [76,77], hepatocyte growth factor (HGF) [78], epidermal growth factor (EGF) [79], platelet-derived growth factor (PDGF) [80,81], and vascular endothelial growth factor (VEGF) [24,82]– are significantly increased in endometriosis [83]. In addition, studies have shown that there are changes in the Th1/Th2 balance toward Th2 in endometriosis [22,43].

In endometriotic lesions, VEGF induces angiogenesis and its immunostaining was observed in the epithelium of endometriotic implants [84], particularly in hemorrhagic red implants [85]. VEGF is also increased in the peritoneal fluid of women with endometriosis [47]. However, is not yet clarified whether it is produced by endometriotic lesions [84,86], or by activated peritoneal macrophages [24].

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Interleukin (IL)-6 is one of the main cytokines in the inflammatory cascade in endometriosis. It is elevated in the peritoneal cavity and blood of these patients, and it is correlated with disease activity [64,87]. IL-10 is also a potent modulator of inflammatory responses and immune cell function – as B cells and macrophages – so it is likely that both IL-6 and IL-10 are partially responsible for the aberrant immune regulation observed in endometriosis [20].

IL-6 can inhibit the proliferation of endometrial stromal cells [88], but it has been shown that in endometriotic lesions, these cells are resistant to IL-6, showing no inhibitory response [89,90]. This cytokine induces T cell activation and differentiation of B lymphocytes into antibody-producing plasma cells, and it can lead to polyclonal B cell stimulation in autoimmune diseases [3]. IL-1 is another cytokine that affects B cells and production of antibodies in addition to increasing prostaglandins, collagen, and tissue repair [5,19].

IL-1 and TNF-α usually initiate the cascade of cytokines and inflammatory response. TNF-α is increased in the peritoneal fluid of women with endometriosis, and it has higher concentrations in the later stages of the disease [91]. It has been suggested that it may contribute to the adhesion of endometrial cells to the peritoneal cavity [92].

IL-8 is also increased in endometriosis [72,73]. IL-8 contributes to cell adhesion [65] and is a potent angiogenic factor [3]. IL-8 stimulates the growth of topic and ectopic endometrial cells [73], probably through TNF-α activation [93]. It is produced by the mesothelium as a response to proinflammatory cytokine stimuli. IL-8 levels can be correlated to the severity of the disease [72].

Concerning the IL-10 family, it was demonstrated that IL-19 and IL-22 are both significantly decreased in the sera of women with ovarian endometrioma without deep infiltrating endometriosis [94]. In addition, there was a reverse correlation between levels of these cytokines and the occurrence of deep dyspareunia in those patients. The authors concluded that these anti-inflammatory cytokines exert immunosuppressive effects favorable to the development of ovarian endometrioma.

IL-13 is another anti-inflammatory cytokine that was shown to be decreased in endometriosis. It is a potent regulator of macrophage activation; hence, its reduction in the peritoneal fluid of women with endometriosis could contribute to the pathogenesis of the disease [95].

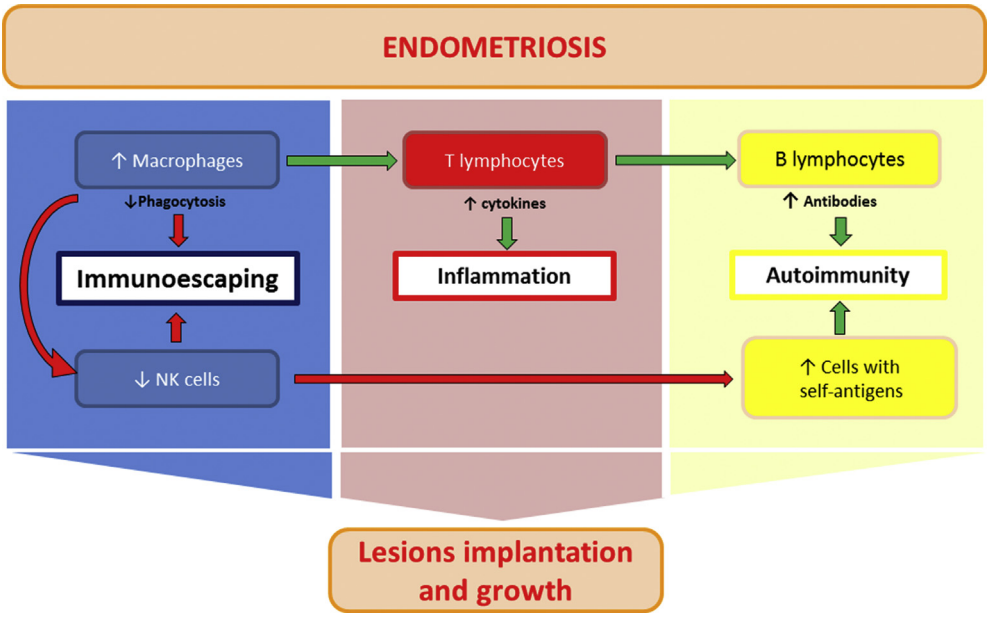

Fig. 1. Immune response in endometriosis.

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The cytokine production in the immune system works in a cascade mode, the biosynthesis of one type of cytokine activates the production of a whole group of inflammatory mediators. In addition, each cytokine has different target tissues and biologic effects, which makes more difficult to clarify the role of a specific mediator in the development of endometriosis. It has also been shown that they can be produced by endometriotic cells, mesothelium, and other resident cells in the peritoneal cavity [87,96]. Cytokines are also deregulated in the peripheral blood of women with endometriosis, suggesting a systemic effect of the disease [3,94,97].

Summary

Even if the pathophysiology of endometriosis is not completely understood, it is well established that the immune system plays a key role in this disease. There is substantial evidence of aberrant function of almost all types of immune cells in women with endometriosis with decreased T cell reactivity and NK cytotoxicity, polyclonal B cells activation and increased antibody production, increased number and activation of peritoneal macrophages, and changes in inflammatory mediators (Fig. 1). In addition, some alterations are similar to those observed in autoimmune diseases [23].

New clinical treatments for endometriosis are an urgent need, especially nonhormonal drugs. Most of the current therapies are contraceptive, and women with endometriosis may have to choose between managing the pain and trying to conceive [62].

The ability of ectopic endometrial cells to escape apoptosis and cell-mediated destruction to later achieve peritoneal adhesion and invasion may be a target to new nonhormonal therapies for endometriosis. However, these mechanisms should be more deeply understood to make possible the design therapeutic strategies [3].

Practice points

- The physiopathology of endometriosis is not completely understood. There seems to be a peritoneal environment that allows the proliferation of ectopic endometrial cells associated with an aberrant immune response.
- There is substantial evidence of aberrant function of almost all types of immune cells in women with endometriosis: decreased T cell reactivity and NK cytotoxicity; polyclonal activation of B cells and increased antibody production; increased number and activation of peritoneal macrophages; and changes in inflammatory mediators.
- New clinical treatments for endometriosis are an urgent need, especially nonhormonal drugs. The study of immunology may clarify its role in the pathogenesis of endometriosis and contribute to the development of new therapeutic strategies.

Research agenda

- Further studies of the immunology of endometriosis could help clarifying the pathophysiology of the disease and lead to the development of new treatments.
- The ability of ectopic endometrial cells to escape apoptosis and cell-mediated destruction to later achieve peritoneal adhesion and invasion may be a target to new nonhormonal therapies for endometriosis. However, these mechanisms should be more deeply understood to make possible the design of therapeutic strategies.

Conflicts of interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or nonfinancial interest in the subject matter or materials discussed in this manuscript.

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