Pathogenesis of endometriosis: natural immunity dysfunction or autoimmune disease?

Giuseppe Matarese[1], Giuseppe De Placido[2], Yorgos Nikas[3] and Carlo Alviggi[2]

[1]Gruppo di ImmunoEndocrinologia, Istituto di Endocrinologia e Oncologia Sperimentale, Consiglio Nazionale delle Ricerche (IEOS-CNR) and Cattedra di Immunologia, Dipartimento di Biologia e Patologia Cellulare e Molecolare, Università di Napoli 'Federico II', Via S. Pansini, 5–80131 Napoli, Italy
[2]Dipartimento di Scienze Ostetriche, Ginecologiche, Urologiche e Medicina della Riproduzione, Università di Napoli 'Federico II', Napoli, Italy
[3]Second Department of Obstetrics and Gynecology, Aretaieio University Hospital, Athens, Greece

Endometriosis is a chronic inflammatory disease, characterized by implantation and growth of endometrial tissue outside the uterine cavity. This disabling condition is considered one of the most frequent diseases in gynecology, affecting 15–20% of women in their reproductive life. Pelvic endometriosis, the most common form of the disease, is associated with increased secretion of pro-inflammatory cytokines, neoangiogenesis, intrinsic anomalies of the refluxed endometrium and impaired function of cell-mediated natural immunity. Recently, endometriosis has also been considered to be an autoimmune disease, owing to the presence of autoantibodies, the association with other autoimmune diseases and recurrent immune-mediated abortion. These findings are in apparent contradiction with the reduced cell-mediated natural immunity observed during the disease. In this review, we focus on the multiple processes underlying the complex pathogenesis of endometriosis, with particular emphasis on the role played by the immune system with the induction of autoimmunity.

Endometriosis is classically described as the presence of endometrial tissue (glandular epithelium and stroma) outside the uterine cavity. It is a benign chronic inflammatory disease, associated with pain (chronic pelvic pain, progressive dysmenorrhea and dyspareunia) and infertility. The most common form of this disorder, pelvic endometriosis (PE), affects 15–20% of all women in their reproductive life, and 30–50% of infertile patients. Endometriotic foci can be found anywhere in the pelvis, including the peritoneal surface of endopelvic structures and of the ovaries [1,2].

Two different theories have been proposed for the pathogenesis of PE: the implantation theory and the metaplasia theory [3,4]. The implantation theory considers the *primum movens* of the process to be retrograde menstruation, during which eutopic endometrial cells reflux throughout the tubes to the peritoneal cavity, adhere to the peritoneal wall, proliferate and form endometriotic lesions (Figs 1 and 2) [3,4]. Retrograde menstruation is then a continuous source of cells for maintenance of the disease. The metaplasia theory hypothesizes that there is a sex-hormone-dependent transformation of peritoneal cells into Müllerian-type epithelium, at least in some cases of endometriosis [4]. This might explain evidence of endometriosis in men and in women without menstruation. Although these two hypotheses can be considered complementary, an increasingly large body of evidence supports the implantation theory, which currently represents the most recognized pathogenic model for PE.

Retrograde menstruation occurs in up to 80% of women during their reproductive life; the discrepancy between the incidence of this phenomenon and the occurrence of PE might be explained by the presence of further 'permissive' factors that promote the implantation and growth of endometrial cells [5]. Many potential factors have been investigated, including the biochemical and cellular composition of the peritoneal fluid (PF), the local and systemic immune response, and the characteristics of the refluxed endometrium [1,5]. Recently, endometriosis has also been considered to be an autoimmune disease, because it is often associated with the presence of autoantibodies, other autoimmune diseases and recurrent immune-mediated abortion [6–8]. In this review, we discuss the lines of evidence that link immune system function with the pathogenesis of endometriosis.

Peritoneal microenvironment and macrophage activity

An abnormal peritoneal microenvironment is thought to be a particularly relevant 'permissive' condition for implantation and growth of refluxed endometrium (Fig. 3) [9]. Alterations in the volume and composition of PF might occur during inflammation, as a result of local production of soluble factors. Experimental evidence regarding the increase in PF volume during PE is controversial. However, PE is a chronic inflammatory condition, and many studies have demonstrated an abnormal local production of pro-inflammatory cytokines,

Corresponding author: Giuseppe Matarese (gmatarese@napoli.com).

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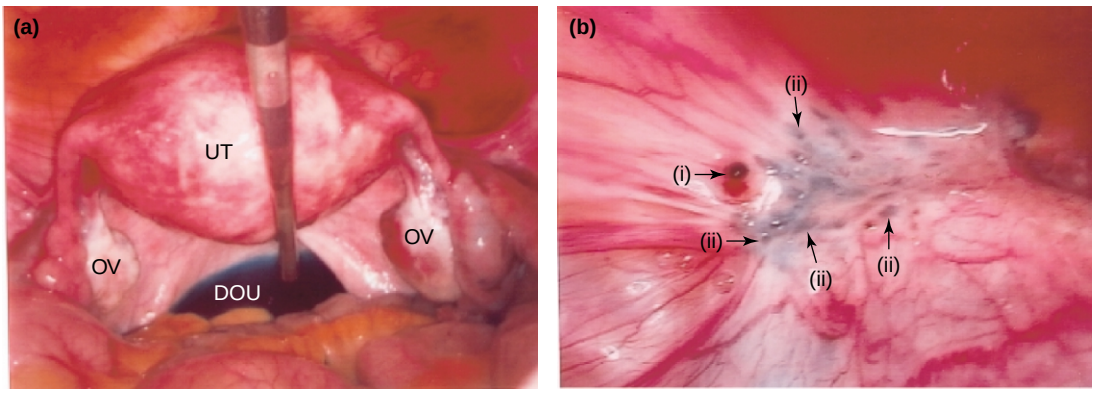

Fig. 1. Laparoscopic images showing a normal pelvis (a) and an area of peritoneum with multiple endometriotic lesions associated with multiple vascular ramifications (b). In the endometriotic peritoneum, two different types of endometriotic foci are visible on the left wall of the pelvis: (i) an early active red-flamed spot, in which the ectopic endometrium can be identified (see Fig. 2c,d for electron microscopy); and (ii) typical blue–black lesions, representing the effect of inflammatory and remodeling processes, in which the ectopic endometrial tissue cannot be always identified, owing to the accumulation of debris and hemosiderin (see Fig. 2e,f for electron microscopy). The magnification in (a) is 10× and in (b) is 16×. Abbreviations: DOU, Douglas patch; OV, ovary; UT, uterus.

such as tumor necrosis factors α (TNF-α), interleukin-1 (IL-1), IL-6 and IL-8 [9–12]. In this complex scenario, it is very difficult to formulate a single pathogenic model for the disease. Different lines of research have been aimed at elucidating the relationship between intra-peritoneal cytokines and the activity of immune-related cells during PE (Fig. 3). Peripheral monocytes and peritoneal macrophages (PM) have been identified as key cells in the regulation and promotion of the process. In particular, PM number, concentration and activation status are enhanced [13,14]. This might simply reflect a physiological inflammatory response to senescent endometrial antigens and/or to cellular debris, accumulating in the peritoneal cavity after cyclic intra-peritoneal microhemorrhage. In some conditions that favor tubal reflux (e.g. cervical stenosis), the accumulation of cells and debris in the peritoneal cavity might be greater than the removal capacity of PM and/or other cells belonging to this scavenging and disposal system. Nevertheless, it could be hypothesized that genetically or environmentally determined factors that enhance PM activity might account for an increased susceptibility to the disease (Fig. 3). This notion is supported by evidence of increased production of IL-6 and IL-8 by peripheral blood monocytes in women with PE, when compared with unaffected subjects [11–15]. Other diseases, such as tumors, have been used to identify different macrophage-associated activities. More specifically, it is possible to identify two different polarized subclasses of macrophages that describe a continuum of diverse functional states [16,17]. The available information suggests that classically activated M1 macrophages (i.e. activated by lipopolysaccharide) are potent effector cells that kill microorganisms and tumor cells, and produce copious quantities of pro-inflammatory cytokines [16,17]. By contrast, M2 macrophages tune inflammatory responses and adaptive T helper-1 (Th1) immunity, scavenge debris, and promote angiogenesis, tissue remodeling and repair (Fig. 3) [16,17]. Alteration of the balance between these two subclasses of macrophages might be involved in the pathogenesis of PE, which might in turn cause an increase in the local production of factors promoting angiogenesis and implantation of endometrial cells (Fig. 3). In conclusion, abnormal PM activation might represent a 'permissive' factor or an effect of the implantation and growth of ectopic endometrium. In either case, the increase in the production of growth and angiogenic factors, as well as of various cytokines, might be responsible for maintenance of the disorder and impairment of reproductive function [16–19].

Features of the endometrium

An expanding body of evidence supports the hypothesis that constitutive and/or acquired characteristics of the eutopic endometrium favor its survival, adhesion and growth outside the uterine cavity. Recent reports suggest that endometrial cells from women with PE show a decrease in apoptosis and in sensitivity to macrophage-mediated cytolysis (Fig. 3) [20,21]. Indeed, an increase in endometrial expression of the anti-apoptotic gene, *Bcl-2*, has been demonstrated in such patients [20,21]. Abnormal expression of genes encoding adhesion molecules also occurs during PE [22]. In particular, endometrial cells from these subjects appear to produce and shed increased amounts of the soluble intercellular adhesion molecule 1 (sICAM-1) [22,23]. Eutopic endometrium from patients with endometriosis might be more invasive and prone to peritoneal implantation, as a result of altered production of proteolytic enzymes such as matrix metalloproteinases (MMPs) [24,25]. More specifically, these endometrial cells show higher levels of MMP-2 and membranous type-1 MMP, and lower levels of the tissue inhibitor of MMP-2 [25]. In addition, an enhanced angiogenic activity might play a key role in the development and maintenance of peritoneal lesions (Figs 1b and 3) [26]. In this regard, it is worth noting that an increase in the expression of the gene encoding vascular endothelial growth factor (VEGF) has been reported in the eutopic and ectopic endometrium of patients with PE [26–29]. Anomalies of the refluxed endometrium could represent a primary or constitutive

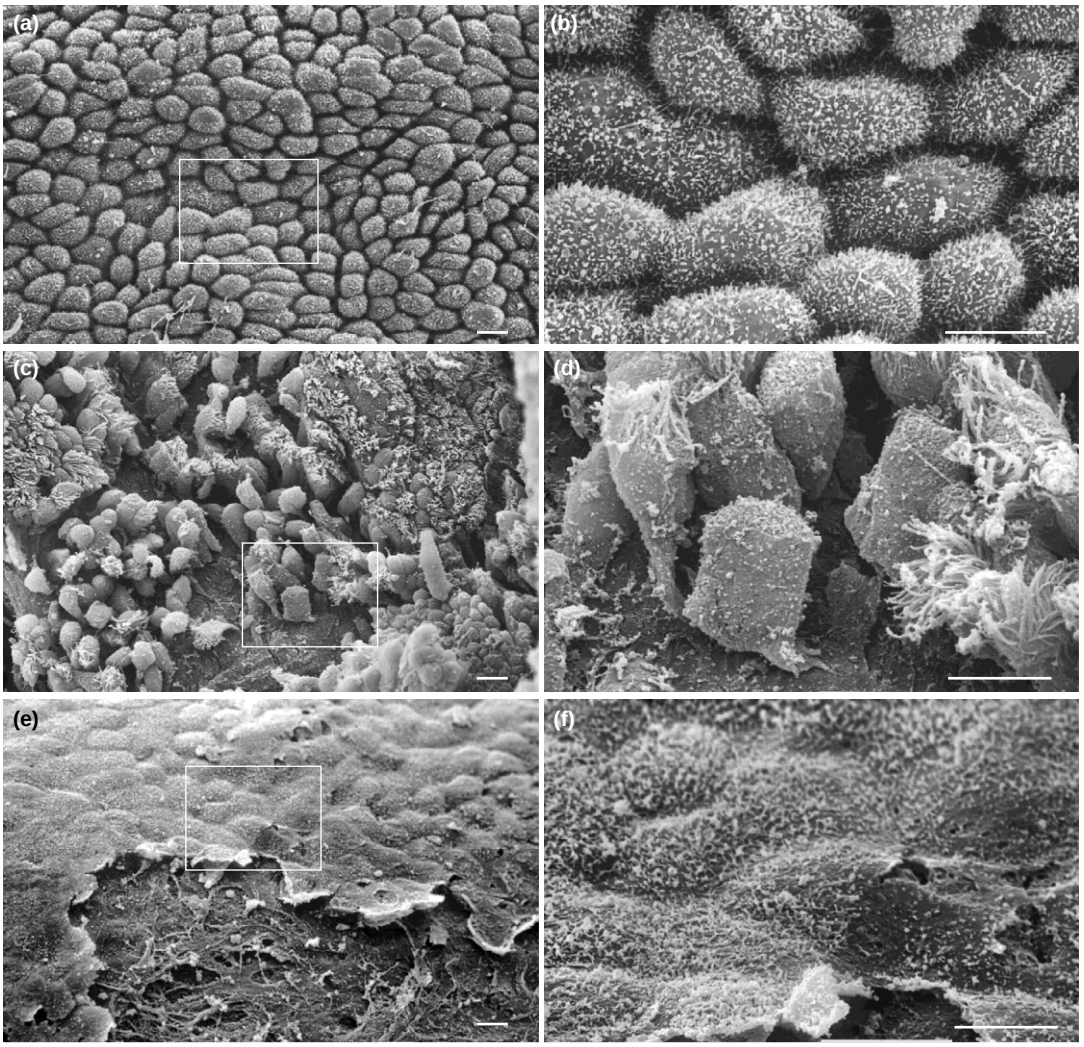

Fig. 2. (a) Scanning electron micrograph of normal peritoneum. A complete sheath of mesothelial cells is covering the peritoneal surface. (b) Closer view of the boxed area in panel (a), showing that the mesothelial cells are covered with short and thick microvilli and have a cobblestone appearance. (c) Scanning electron micrograph of an active lesion, classified as a red-flamed spot (see Fig. 1b). In the upper left and right of the panel, epithelial implants of secretory and ciliated cells are present, forming a complete sheath. In the remaining areas, the cells are degenerating and detaching, exposing the underlying peritoneal surface. (d) Closer view of the boxed area in panel (c). Degenerative changes of the epithelial cells are evident, including rounding of their shape, loosening of their attachment to the substratum, an absence of microvilli, and decilliation. The substratum (the connective tissue of the peritoneum) appears covered with a fibrinous/amorphous material. (e) Scanning electron micrograph of a lesion classified as blue–black spot (see Fig. 1b). Two distinct areas are visible: the upper and left parts of the panel show an area covered by a sheath of flattened mesothelial cells. In the lower right of the panel, the mesothelial cells are absent, exposing the underlying loose connective tissue, which appears to be covered with a fibrinous/amorphous material, probably resulting from inflammatory reaction. (f) Closer view of the boxed area in panel (e). The mesothelial cells are flat and covered with amorphous material. The plasma membranes in some areas appear thinned. Scale bars in all panels represent 10 μm.

'permissive' condition or the effect of local cytokines. The levels of different factors (e.g. leptin, IL-6 and TNF-α) that are potentially able to regulate and/or promote the activity of the above-mentioned molecules in endometrial cells, are increased in PE [30–32].

Endometriosis and the immune response: the role of natural killer cells

Various lines of evidence suggest that both peripheral and peritoneal natural killer (NK) lymphocytes from women with PE display reduced cytotoxicity against autologous endometrium and heterologous cell systems [33–35]. As a result, it has been suggested that NK cells are involved in a peritoneal cytolysis and scavenging system that is able to remove refluxed endometrial tissue (Fig. 3). By contrast, a defective system with altered NK and/or PM activities might allow the implantation and growth of endometrial cells within the peritoneal cavity. According to this hypothesis, the NK deficit observed during PE should be interpreted as a primitive and probably constitutive phenomenon, accounting for the establishment of the disease. Nevertheless, another possible interpretation has been recently proposed: the decrease in NK activity represents an epiphenomenon following the inflammatory response against the ectopic endometrium. Several macrophage-derived factors, such as prostaglandins, sICAM-1 and inhibitory cytokines (e.g. transforming growth factor β) could mediate a secondary modulation of NK cell

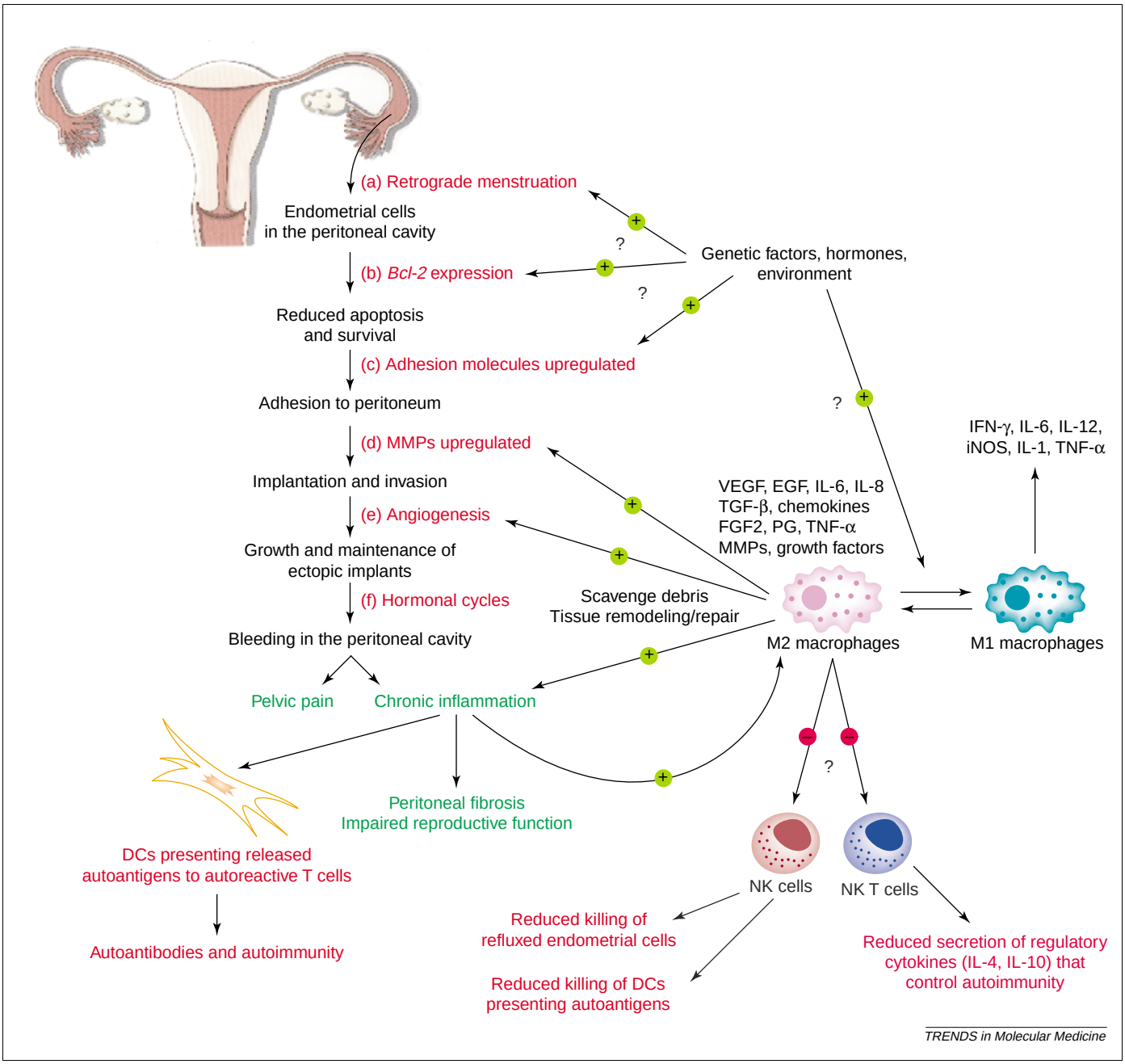

Fig. 3. A simplified view of the different factors that account for the pathogenesis of pelvic endometriosis, with particular emphasis on the role of macrophages, natural killer (NK) cell subsets and the immune system. Shown is the sequence of events leading to the implant, growth and progression of the disease. The peritoneal microenvironment can alter NK cell function in the killing of ectopic endometrium and of dendritic cells (DCs) loaded with autologous antigens. In addition, reduced activity of NK T cells might affect the production of regulatory cytokines, which could in turn contribute to autoimmunity and autoantibody secretion. Abbreviations: EGF, epidermal growth factor; FGF, fibroblast growth factor; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; MMP, matrix metalloproteinase; PG, prostaglandin; TGF, transforming growth factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

activity (Fig. 3). This hypothesis is also supported by evidence suggesting that serum and PF of women with endometriosis can suppress NK cytotoxicity in normal individuals [36,37]. In addition, treatment with gonadotropin-releasing hormone (GnRH) agonists restores NK cell activity in patients with PE, which might be due to a direct effect on immune cells or to an indirect action via the reduction of peritoneal microhemorrhages [38].

Natural immunity dysfunction or autoimmune disease?

Endometriosis is considered to be an autoimmune disease because it fulfills most of the classification criteria for such disorders. Specifically, it presents with tissue damage, production of autoantibodies (against endometrium, ovary, phospholipids and histones), association with other autoimmune diseases, and recurrent immune-mediated abortion [8,39,40]. Autoimmune diseases, which affect ~5% of the population and disproportionately affect women, comprise a heterogeneous group of poorly understood disorders. They are characterized by the presence of abnormal T- and B-lymphocyte activation, although non-lymphoid cells, particularly antigen-presenting cells (APCs) such as macrophages and dendritic cells (DCs), also contribute to pathogenesis, by presenting autoantigens

to autoreactive T cells in the context of the major histocompatibility complex. Genetic, hormonal and environmental factors also have a role in the pathogenesis of autoimmune diseases [41].

In the case of PE, an enhanced immune response against self-antigens is in apparent contradiction with reduced NK-mediated cytotoxicity, which should be associated with an impaired immune response and an increased susceptibility to infections [42]. However, recent evidence might explain this association between NK dysfunction and autoimmunity during PE [43,44].

To better understand these aspects, it must be remembered that the immune response is classically divided in the natural (innate) and adaptive arms. Natural immunity is characterized by immediately available phagocytic cells, such as granulocytes, monocytes and macrophages. These cells are able to combat a wide range of pathogens without requiring any previous exposure. By contrast, adaptive (also known as specific) immunity is characterized by an antigen-specific response: T and B lymphocytes produce cytokines and antibodies as result of their activation, following antigen recognition via their specific receptors. The adaptive immune response confers lifelong protection against re-infection by the same pathogen, a capability that distinguishes such responses from natural immunity. Together, the natural and adaptive immune systems provide a remarkably effective defense system, ensuring that we only rarely become ill, even though we are surrounded by potentially pathogenic microorganisms. These two systems are strictly interdependent and an impairment of either can affect efficiency and cause dysregulation of the immune response as a whole [45].

Although NK cells were first characterized by their ability to kill particular tumor cell lines *in vitro* without the need for previous immunization or activation, it is now known that they represent a key interface between the innate and adaptive immune response [42]. Over the past few years, it has been shown that these cells can be divided into different subclasses. Classically, NK cells do not express the T-cell receptor (TCR)–CD3 membrane complex, and can be identified by the presence of CD16 and CD56 molecules. Another subset of NK cells, known as NK T cells, express not only CD16 but also the TCR–CD3 complex. These cells constitute 15–20% of the NK cell population, and are characterized by the capacity both to kill cell targets and to secrete cytokines, including IL-4 and IL-10, which are important in the control of autoimmunity [42–44]. Typical CD16/CD56 NK cells have been shown to kill autologous DCs presenting self-antigens to autoreactive T cells [46,47]. Taken together, these lines of evidence suggest that NK cells play a key role in the delicate balance of immune self-tolerance, by eliminating potentially dangerous cells presenting self-antigens. Hence, the reduced NK activity during endometriosis could at least in part explain the increased autoimmune reactivity associated with the disease: in the peritoneal cavity, NK cells might be less effective in killing autologous DCs loaded with endometrial self-antigens, facilitating their presentation to autoreactive T cells and the production of autoantibodies (Fig. 3) [46,47]. An altered balance between classical and NK T cells (i.e. a reduction in the number and/or function of the latter) might also contribute to dysregulation of the immune response. In conclusion, altered secretion of regulatory cytokines by NK T cells and/or reduced NK-cell anti-autologous-DC responses, could explain why endometriosis shares common features with autoimmune disease.

Concluding remarks

The immunological aspects of endometriosis represent an intriguing area of study. There is now significant evidence that immune mediators such as cytokines, as well as NK cells and macrophages, might be involved in the pathogenesis of the disease. These data support the idea that endometriosis can be considered as an autoimmune disorder, associated with a dysfunction of natural immunity [8]. Recently, there has been increasing interest in factors that work at the interface between natural and adaptive immune responses. In this context, endometriosis seems to represent an optimal human model for understanding how NK activity can modulate and/or promote autoimmunity [42,43]. The relationship between the endocrine and the immune systems has been the subject of intense research for decades [48]. Endometriosis seems to display the characteristics of a hormone-dependent and immune-related disorder, in which hormonal modulation is effective in the treatment of inflammation-dependent symptoms. Although the efficacy of GnRH agonists appears to be related mainly to the subsequent reduction of estrogen activity, there is evidence that these drugs exert a direct immunomodulatory effect during PE [38]. Indeed, studies of autoimmune disease have clearly demonstrated that hormones previously known for their functions in the regulation of reproduction and metabolism are also modulators of the natural and adaptive immune responses. For instance, prolactin and leptin, whose activities are increased in women with PE, have been shown to contribute to gender-related autoimmune disease susceptibility [32,49–52]. Again, endometriosis seems to represent an important human model of disease in which hormones, cytokines and the immune system influence each other. To date, the conventional treatment for this disease has been based on hormonal suppression and/or surgical removal of lesions. Such therapeutic interventions are effective in the treatment of symptoms, including pain and infertility. Study of the relationship between the natural and the adaptive immune responses during endometriosis could lead to the development of additional therapeutic immune interventions, such as anti-cytokine antibodies or cytokine-receptor antagonistic ligands, able to produce an effective and long-lasting treatment.

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References

1 Oral, E. and Arici, A. (1997) Pathogenesis of endometriosis. *Obstet. Gynecol. Clin. North Am.* 24, 219–233
2 Goldman, M.B. and Cramer, D.W. (1990) The epidemiology of endometriosis. *Prog. Clin. Biol. Res.* 323, 15–31
3 Sampson, J.A. (1927) Peritoneal endometriosis due to menstrual dissemination of endometrial tissue into the peritoneal cavity. *Am. J. Obstet. Gynecol.* 14, 422–469
4 Koninckx, P.R. *et al.* (1999) Implantation versus infiltration: the Sampson versus the endometriotic disease theory. *Gynecol. Obstet. Invest.* 47, 3–9
5 Melega, C. *et al.* (1991) Tissue factors influencing growth and maintenance of endometriosis. *Ann. New York Acad. Sci.* 622, 256–265
6 Vinatier, D. and Dufour, P. (1997) Is endometriosis an immunological disease? *Contracept. Fertil. Sex* 25, 179–191
7 Iborra, A. *et al.* (2000) Autoimmune response in women with endometriosis. *Am. J. Reprod. Immunol.* 44, 236–241
8 Nothnick, W.B. (2001) Treating endometriosis as an autoimmune disease. *Fertil. Steril.* 76, 223–231
9 Koninckx, P.R. *et al.* (1998) Endometriotic disease: the role of peritoneal fluid. *Hum. Reprod. Update* 4, 741–751
10 Akoum, A. *et al.* (2002) Estradiol and interleukin-1β exert a synergistic stimulatory effect on the expression of the chemokine regulated upon activation, normal T cell expressed, and secreted in endometriotic cells. *J. Clin. Endocrinol. Metab.* 87, 5785–5792
11 Piva, M. *et al.* (2001) Interleukin-6 differentially stimulates haptoglobin production by peritoneal and endometriotic cells *in vitro*: a model for endometrial-peritoneal interaction in endometriosis. *J. Clin. Endocrinol. Metab.* 86, 2553–2561
12 Sakamoto, Y. *et al.* (2003) Tumor necrosis factor-β-induced interleukin-8 (IL-8) expression in endometriotic stromal cells, probably through nuclear factor-κB activation: gonadotropin-releasing hormone agonist treatment reduced IL-8 expression. *J. Clin. Endocrinol. Metab.* 88, 730–735
13 Zeller, J.M. *et al.* (1987) Enhancement of human monocyte and peripheral macrophage chemioluminescence activities in women with endometriosis. *Am. J. Reprod. Immunol. Microbiol.* 13, 78–82
14 Halme, J. *et al.* (1984) Accentuated cyclic activation of peritoneal macrophages in patients with endometriosis. *Am. J. Obstet. Gynecol.* 148, 85–90
15 Dunselman, G.A.J. *et al.* (1988) Functional aspects of peritoneal macrophages in endometriosis of women. *J. Reprod. Fertil.* 82, 707–710
16 Mantovani, A. *et al.* (2002) Macrophage polarization: tumor-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes. *Trends Immunol.* 11, 549–555
17 Mills, C.D. *et al.* (2000) M-1/M-2 macrophages and the Th1/Th2 paradigm. *J. Immunol.* 164, 6166–6173
18 Haney, A.F. *et al.* (1981) Peritoneal fluid cell populations in infertility patients. *Fertil. Steril.* 35, 696–698
19 Halme, J. *et al.* (1982) Pelvic macrophages in normal and infertile women: the role of patent tubes. *Am. J. Obstet. Gynecol.* 142, 890–895
20 Meresman, G.F. *et al.* (2000) Apoptosis and expression of *Bcl-2* and *Bax* in eutopic endometrium from women with endometriosis. *Fertil. Steril.* 74, 760–766
21 Jones, R.K. *et al.* (1998) Apoptosis and *bcl-2* expression in normal human endometrium, endometriosis and adenomyosis. *Hum. Reprod.* 13, 3496–3502
22 Somigliana, E. *et al.* (1996) Human endometrial stromal cells as a source of soluble intercellular adhesion molecule (ICAM)-1 molecules. *Hum. Reprod.* 11, 1190–1194
23 De Placido, G. *et al.* (1998) Serum concentrations of soluble human leukocyte class I antigens and of the soluble intercellular adhesion molecule-1 in endometriosis: relationship with stage and non-pigmented peritoneal lesions. *Hum. Reprod.* 13, 3206–3210
24 Starzinski-Powitz, A. *et al.* (1999) The putative role of cell adhesion molecules in endometriosis: can we learn from tumour metastasis? *Mol. Med. Today* 5, 304–309
25 Chung, H.W. *et al.* (2002) Matrix metalloproteinase-2, membranous type 1 matrix metalloproteinase, and tissue inhibitor of metalloproteinase-2 expression in ectopic and eutopic endometrium. *Fertil. Steril.* 78, 787–795
26 Healy, D.L. *et al.* (1998) Angiogenesis: a new theory for endometriosis. *Hum. Reprod. Update* 4, 736–740
27 Tan, X.J. *et al.* (2002) Expression of vascular endothelial growth factor and thrombospondin-1 mRNA in patients with endometriosis. *Fertil. Steril.* 78, 148–153
28 McLaren, J. (2000) Vascular endothelial growth factor and endometriotic angiogenesis. *Hum. Reprod. Update* 6, 45–55
29 Donnez, J. *et al.* (1998) Vascular endothelial growth factor (VEGF) in endometriosis. *Hum. Reprod.* 13, 1686–1690
30 Park, H.Y. *et al.* (2001) Potential role of leptin in angiogenesis: leptin induces endothelial cell proliferation and expression of matrix metalloproteineses *in vivo* and *in vitro*. *Exp. Mol. Med.* 33, 95–102
31 Zhang, R.J. *et al.* (1993) Effect of TNF-α on adhesion of human endometrial cells to peritoneal mesothelial cells: an *in vitro* system. *Fertil. Steril.* 59, 1196–1201
32 Matarese, G. *et al.* (2000) Increased leptin levels in serum and peritoneal fluid of patients with pelvic endometriosis. *J. Clin. Endocrinol. Metab.* 85, 2483–2487
33 Oosterlynck, D.J. *et al.* (1991) Women with endometriosis show a defect in natural killer activity resulting in a decreased cytotoxicity to autologous endometrium. *Fertil. Steril.* 56, 45–51
34 Wilson, T.J. *et al.* (1994) Decreased natural killer cell activity in endometriosis patients: relationship to disease pathogenesis. *Fertil. Steril.* 62, 1086–1088
35 Dmowski, W.P. *et al.* (1981) Deficient cellular immunity in endometriosis. *Am. J. Obstet. Gynecol.* 141, 377–383
36 Kanzaki, H. *et al.* (1992) Suppression of natural killer cell activity by sera from patients with endometrioisis. *Am. J. Obstet. Gynecol.* 167, 257–261
37 Oosterlynck, D.J. *et al.* (1993) Immunosuppressive activity of peritoneal fluid in women with endometriosis. *Obstet. Gynecol.* 82, 206–212
38 Hsu, C. *et al.* (1997) Immunomodulation in women with endometriosis receiving GnRH agonist. *Obstet. Gynecol.* 89, 993–998
39 Mathur, S. *et al.* (1982) Autoimmunity to endometrium and ovary in endometriosis. *Clin. Exp. Immunol.* 50, 259–266
40 Badaway, S.Z. *et al.* (1990) Endometrial antibodies in serum and peritoneal fluid of infertile patients with and without endometriosis. *Fertil. Steril.* 53, 930–932
41 O'Shea, J. *et al.* (2002) Cytokines and autoimmunity. *Nat. Rev. Immunol.* 2, 37–45
42 Moretta, A. (2002) Natural killer cells and dendritic cells: rendezvous in abused tissues. *Nat. Rev. Immunol.* 2, 957–964
43 Takahashi, K. *et al.* (2001) Natural killer type2 bias in remission of multiple sclerosis. *J. Clin. Invest.* 107, R23–R29
44 Wilson, M.T. and Van Kaer, L. (2003) Natural killer T cells as targets for therapeutic intervention in autoimmune diseases. *Curr. Pharm. Des.* 9, 210–220
45 Murphy, K.M. and Reiner, S.L. (2002) The lineage decisions of helper T cells. *Nat. Rev. Immunol.* 2, 933–944
46 Carbone, E. *et al.* (1999) Recognition of autologous dendritic cells by human NK cells. *Eur. J. Immunol.* 29, 4022–4029
47 Wilson, J.L. *et al.* (1999) Targeting of human dendritic cells by autologous NK cells. *J. Immunol.* 163, 6365–6370
48 Blalock, J.E. (1990) Molecular mechanisms of bidirectional communication between the immune and neuroendocrine systems. *Int. J. Neurosci.* 51, 363–364
49 Peeva, E. *et al.* (2003) Prolactin modulates naive B cell repertoire. *J. Clin. Invest.* 111, 275–283
50 Machida, T. *et al.* (1997) Prolactin secretion in endometriotic patients. *Eur. J. Obstet. Gynecol. Reprod. Biol.* 72, 89–92
51 Cunha-Filho, J.S. *et al.* (2001) Hyperprolactinemia and luteal insufficiency in infertile patients with mild and minimal endometriosis. *Horm. Metab. Res.* 33, 216–220
52 Matarese, G. *et al.* (2001) Leptin potentiates experimental autoimmune encephalomyelitis in SJL female mice and confers susceptibility to males. *Eur. J. Immunol.* 31, 1324–1332