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Immunology of endometriosis

Luiza da Gama Coelho Riccio, MD [a, c, *], Pietro Santulli, MD, PhD [b, c], Louis Marcellin, MD, PhD [b, c], Mauricio Simões Abrão, MD, PhD, Professor [a], Frederic Batteux, MD, PhD, Professor [c, d], Charles Chapron, MD, PhD, Professor [b, c]

[a] *Endometriosis Division, Obstetrics and Gynecology Department, Hospital das Clinicas, School of Medicine, University of São Paulo (USP), São Paulo, Brazil*
[b] *Université Paris Descartes, Sorbonne Paris Cité, Faculté de Médecine, Assistance Publique - Hôpitaux de Paris (AP-HP), Hôpital Universitaire Paris Centre (HUPC), Centre Hospitalier Universitaire (CHU) Cochin, Department of Gynecology Obstetrics II and Reproductive Medicine, Paris, France*
[c] *Department of Development, Reproduction and Cancer, Institut Cochin, INSERM U1016, Equipe Pr Batteux, Université Paris Descartes, Sorbonne Paris Cité, Paris, France*
[d] *Department of Immunology, Hôpital Cochin, AP-HP, Paris, France*

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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

* Corresponding author. Av. Dr. Enéas de Carvalho Aguiar, 255, Cerqueira César CEP 05403-000, São Paulo, Brazil.
E-mail addresses: luiza.riccio@gmail.com (L.G.C. Riccio), pietro.santulli@aphp.fr (P. Santulli), louis.marcellin@gmail.com (L. Marcellin), msabrao@mac.com (M.S. Abrão), frederic.batteux@aphp.fr (F. Batteux), charles.chapron@aphp.frs (C. Chapron).

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

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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