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Pathogenetic Mechanisms of Deep Infiltrating Endometriosis

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Abstract

Endometriosis is a benign gynecologic disease, affecting women of reproductive age associated with chronic pelvic pain, dysmenorrhea, dyspareunia and infertility. Ovarian endometrioma (OMA), superficial peritoneal endometriosis (SPE), and deep infiltrating endometriosis (DIE) are, till now, recognized as major phenotypes. The discussion is to know whether they share the same pathogenetic mechanisms. Till today, DIE is recognized as the most severe clinical form of endometriosis and has a complex clinical management. The DIE lesions have been considered in the present article, without distinguishing between the anterior (bladder) or the posterior (vagina, uterosacral ligaments, rectum, and ureter) compartment. The present knowledge indicates that hormonal function (estrogen and progesterone receptors) and immunological factors, such as peritoneal macrophages, natural killer cells, and lymphocytes, are critically altered in DIE. The aggressive behavior of DIE may be explained by the highly decreased apoptosis (nuclear factor kappa-light-chain-enhancer of activated B cells [NF-kB], *B-cell lymphoma 2* [Blc-2], and anti-Mullerian hormone) and by the increased proliferation activity related to oxidative stress (NF-kB, reactive oxygen species, extracellular regulated kinase (ERK), advanced oxidation protein product). Invasive mechanisms are more expressed (matrix metalloproteinases and activins) in DIE in comparison to the OMA and SPE. Correlated with the increased invasiveness are the data on very high expression of neuroangiogenesis (nerve growth factor, vascular endothelial growth factor, and intercellular adhesion molecule) genes in DIE. Therefore, at the present time, several of the DIE pathogenetic features result specific in comparison to other endometriosis phenotypes, pleading for the existence of a specific entity. These evidence of specific pathogenetic features of DIE may explain the more severe symptomatology related to this form of endometriosis and suggest possible future target medical treatments.

Keywords

deep infiltrating endometriosis, endometrioma, peritoneal endometriosis, pathogenesis, inflammation, oxidative stress, neuroangiogenesis, apoptosis, pelvic pain

Introduction

Endometriosis is a benign gynecologic disease, characterized by the presence and growth of functional endometrial-like tissue outside uterus, affecting women of reproductive age. The origin of the endometriotic cells is:

(A) *Retrograde menstruation:* Endometrial fragments migrate through fallopian tubes during menstruation.[1]

(B) *Blood and lymphatic dissemination:* Viable endometrial cells travel from endometrium through lymphatic or blood circulation, giving rise to endometriosis in a similar manner to the metastasis of tumor cells.[2,3,4]

(C) *Stem cells:* Endometrium-derived stem/progenitor cells residing in the basalis layer are shed through fallopian tubes to peritoneal cavity during menses and implant, representing probably more severe endometriotic lesions.[5,6]

(D) *Metaplasia of coelomic epithelium:* Peritoneal mesothelial cells differentiate into endometrium-like tissue, and endometrium and coelom have the same origin and their differentiation is under the sex hormones control, primarily estrogen.[7]

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Endometrial cells invade tissues outside the uterine cavity and they grow leading to the formation of "endometriotic lesions" (ie, ectopic endometrium) causing pain (dysmenorrhea, dyspareunia, and pelvic pain) and/or infertility.[7,8] Ovary, rectovaginal septum, bowel, bladder, ureter, and peritoneum are the most common localizations[9] and accordingly 3 different phenotypes are described: (1) ovarian endometrioma (OMA); (2) superficial peritoneal endometriosis (SPE); and (3) deep infiltrating endometriosis (DIE).

Independent of the origin, ectopic endometrial cells undergo biological and molecular changes, and most of the previous studies did not distinguish the various endometriotic phenotypes at the time of specimen collection. Therefore, pathogenetic mechanisms were evaluated as a mix of lesions. The mechanisms driving to the OMA formation have been recently reviewed,[10,11] and the present review aims to summarize those studies, which explored specifically DIE as a separate entity.

Pathology

Glandular and stromal elements at an extrauterine site and the histologic appearance of endometriosis vary considerably according to the site of growth.[12] Histologic patterns associated with DIE include well-differentiated glandular, pure stromal, glandular or mixed differentiation, and pure undifferentiated glandular pattern,[13] and the last is most frequently associated with DIE.[14] Therefore, it is suggested that undifferentiated endometriotic lesions result from the tissue's resistance to suppressor effects of peritoneal fluid, allowing these endometrial foci to infiltrate more deeply.[14] In all cases, a fibromuscular component is described with DIE.[15] Fibrotic tissue is part of the lesions, and progesterone receptors (PRs) are present not only in glands and stroma but also in smooth muscle cells and fibrosis surrounding the DIE lesions.[16] In the specific case of bowel DIE, lesions infiltrate the large bowel wall preferentially along the nerves, even at a distance from the palpated nodule, while the mucosa is rarely involved.[17] Multifocality of lesions is a major characteristic of DIE.[18]

Estrogen and Progesterone Receptors

According to the most available data, estrogens and PRs play a major role in endometriosis, without difference among OMA, SPE, and DIE.[19] Endometriotic lesions show high estrogen biosynthesis and decreased inactivation: Aromatase, which converts estradiol (E2) from androgens, is upregulated in endometriotic tissue (a mix of OMA, endometriosis implants, and peritoneum) compared with eutopic endometrium,[20] while the expression of 17β-hydrosteroid dehydrogenase type 2 (HSD17B2), responsible for E2 metabolism to less active estrone, is decreased in DIE lesions,[21] while 17β-hydrosteroid dehydrogenase type 1 (HSD17B1) messenger RNA (mRNA) is increased in DIE leading to increased tissue concentration of E2.[21]

The expression of estrogen receptor (ER) β is highly upregulated in endometriotic lesions (a mix of tissues from OMA, DIE, or peritoneal endometriosis was studied) due to a decreased promoter methylation.[22] Studies conducted on mix of endometriotic tissue showed that ERβ suppresses ERα expression, yielding an augmented Erβ–ERα ratio, which may cause a shift from E2 stimulation to E2 inhibition of PR expression[22,23] (Figure 1). This mechanism promotes endometriotic tissue (no indication on the form of endometriosis was given) to become resistant to the progesterone's antiproliferative effects.[24,25] Transcripts for A and B isoforms of PR are dysregulated in eutopic endometrium, whereas in endometriotic lesions (a mix of tissues from OMA, DIE, or peritoneal endometriosis), PR-A transcript is preferentially expressed,[23,24] and progesterone resistance is unable to trigger the expression of HSD17B2 and subsequent estrogen metabolism.[23] The recent observation by Zanatta et al indicates that in rectosigmoid DIE an increased expression of ERα, PR-A, and PR-B mRNA is present, suggesting a different behavior with respect to ovarian and peritoneal endometriosis.[26]

Cytokines, Prostaglandins, and Inflammation

The presence of endometrial stroma and epithelial cells in ectopic localization, such as rectum or vagina, implies survival and proliferation in a hostile microenvironment with a prerequisite of immunotolerance. Sphingosine-1-phosphate (S1P) receptor 1 may endorse these modifications. The S1P axis functions have a hub of numerous stimuli, including growth factors, hormones, chemokines, cytokines, and reactive oxygen species (ROS; Figures 1 and 2).

Nitric oxide and prostaglandin productions, induced by interleukin (IL) 1β, tumor necrosis factor α (TNF-α), and other stimuli, are dependent on S1P generation. Prostaglandin endoperoxide synthase 2 (PTGS2) is overexpressed in DIE lesions as well as in SPE and OMA.[27]

Cytokines have pleiotropic, cytostatic, chemoattractant, or angiogenic effects.[25] Recent study shows increased serum levels of IL-1β and IL-1 receptor type II (IL-1sRII) in DIE, in particular in case of the most severe form with intestinal involvement (Figure 2).[28]

Elevated serum concentrations of IL-33 were associated with DIE lesions (multifocal, with intestinal infiltration).[29] Elevated serum IL-33 concentrations in case of suspected or recognized endometriosis could suggest the diagnosis of DIE and should prompt advise the practitioner to perform an appropriate preoperative imaging work-up in order to evaluate the presence of severe and multifocal deep nodules.[29] Ovarian endometrioma, but not DIE, is associated with increased serum levels of IL-6 and IL-8 and have been measured also as a possible screening tool for predicting this condition.[30] These results clearly plead for the existence of altered balance of the cytokines in the serum of DIE afflicted women (Figures 1 and 2).

Upregulation of PTGS2 expression in patients with endometriosis, with the greatest amount detected in severe stage, increases endometrial cell production of prostaglandin $PGF_2\alpha$ and PGE_2, and prostaglandin pathway is strongly deregulated in endometriosis lesions for the benefit of an increased PTGS2 expression (a mix of SPE, OMA, and DIE; Figure 1).[31] In addition, also prostaglandin receptors (E-series prostaglandin

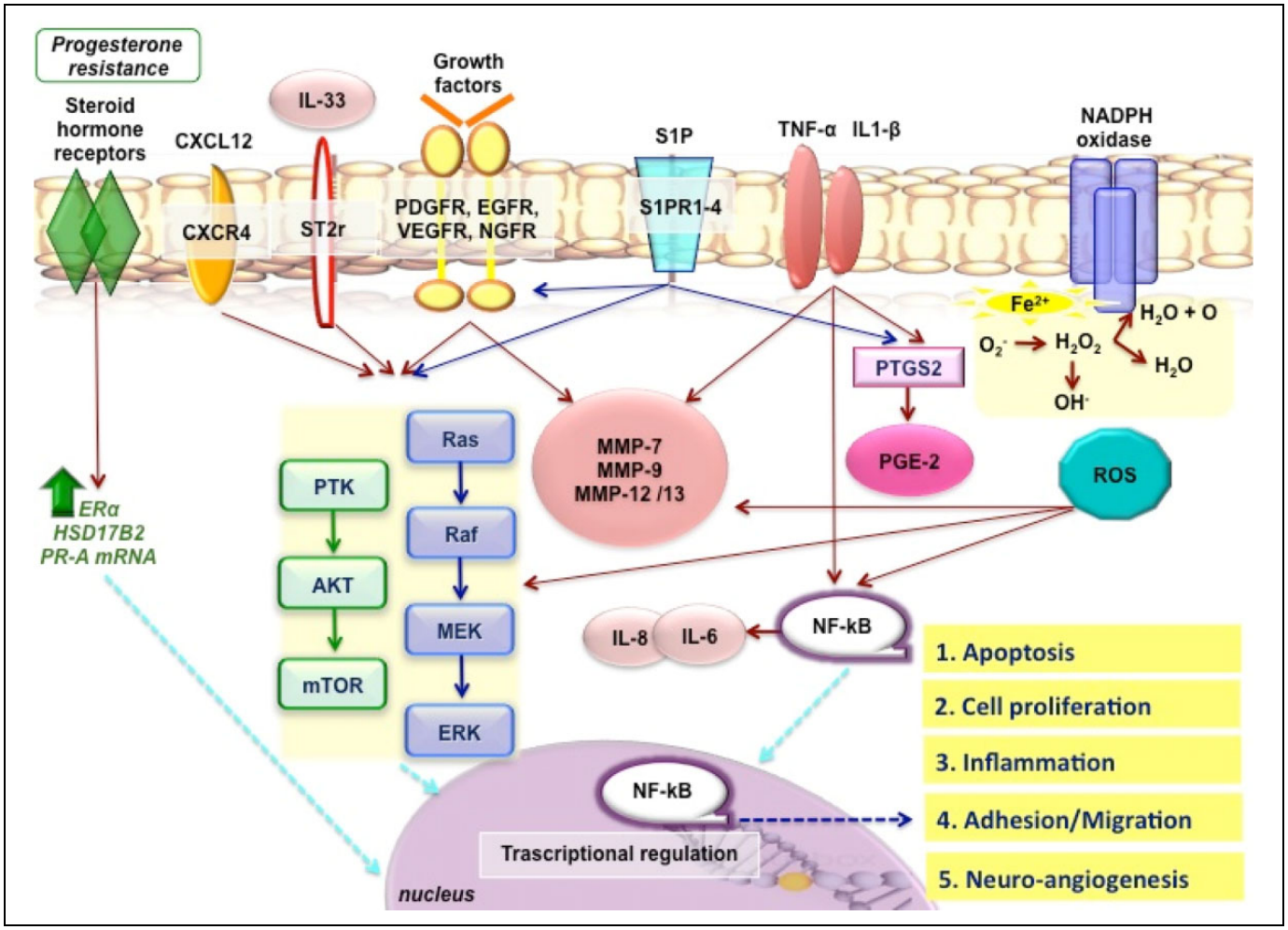

Figure 1. Signaling mechanisms of deep infiltrating endometriosis (DIE) pathogenesis.

receptors [PT-GER]), encoded by 4 different genes, are drastically increased in DIE ectopic lesions.[32] Most interestingly, in recent study, hormonal treatment appears to enhance even more PTGS2 expression supporting the evidence that oral contraceptive use is not efficient to avoid the progression of the disease, especially in DIE cases.[31,33]

Apoptosis

The role of apoptosis in normal endometrium is to eliminate senescent or dysfunctional cells, as a way for tissue repair at each menstrual cycle. In women with endometriosis, endometrial cells regurgitated into the peritoneal cavity lack the appropriate mechanisms of programmed cell death and therefore escape clearance and survive to invade the peritoneum, probably through concomitant overexpression of antiapoptotic factors and reduced expression of proapoptotic factors (Figure 1).[32,34]

The following 3 major mechanisms are involved in the control of cell survival in endometriotic tissue: (1) endometriotic cells respond to estrogen-induced antiapoptotic signaling more intensely than normal cells, and the increased sensitivity of these endometriotic cells to estrogens is related to the abundance of ERβ and contributed to implant survival,[7,25] in addition (2) progesterone resistance of endometriotic lesions causes refractory to progestogen-induced apoptosis.[25] (3) Moreover, NF-kB has antiapoptotic effect and its activation in endometriotic stromal cells is induced by TNF-α and estradiol and inhibited by progestogens, which is an additional downstream mechanism involved in steroid hormone control of apoptosis in endometriosis (a mix of OMA, SPE, and DIE).[35]

Iron, Oxidative Stress, and Cells Proliferation

In addition to a local peritoneal-reduced apoptosis of endometrial cells, the retrograde blood transport delivers iron to macrophages, inducing oxidative injury to cells since iron potentiates oxygen and nitrogen toxicity by generating free radical.[36] High levels of ROS are generated in endometriosis,[37] inducing cell damage and proliferation. Ngô et al have shown on biopsies of eutopic endometrium and biopsies of deep infiltrating endometriotic nodule that formation of superoxide anions, hydrogen peroxide, and nitric oxide have a role in the control endometriotic cell proliferation (Figures 1 and 2).[38]

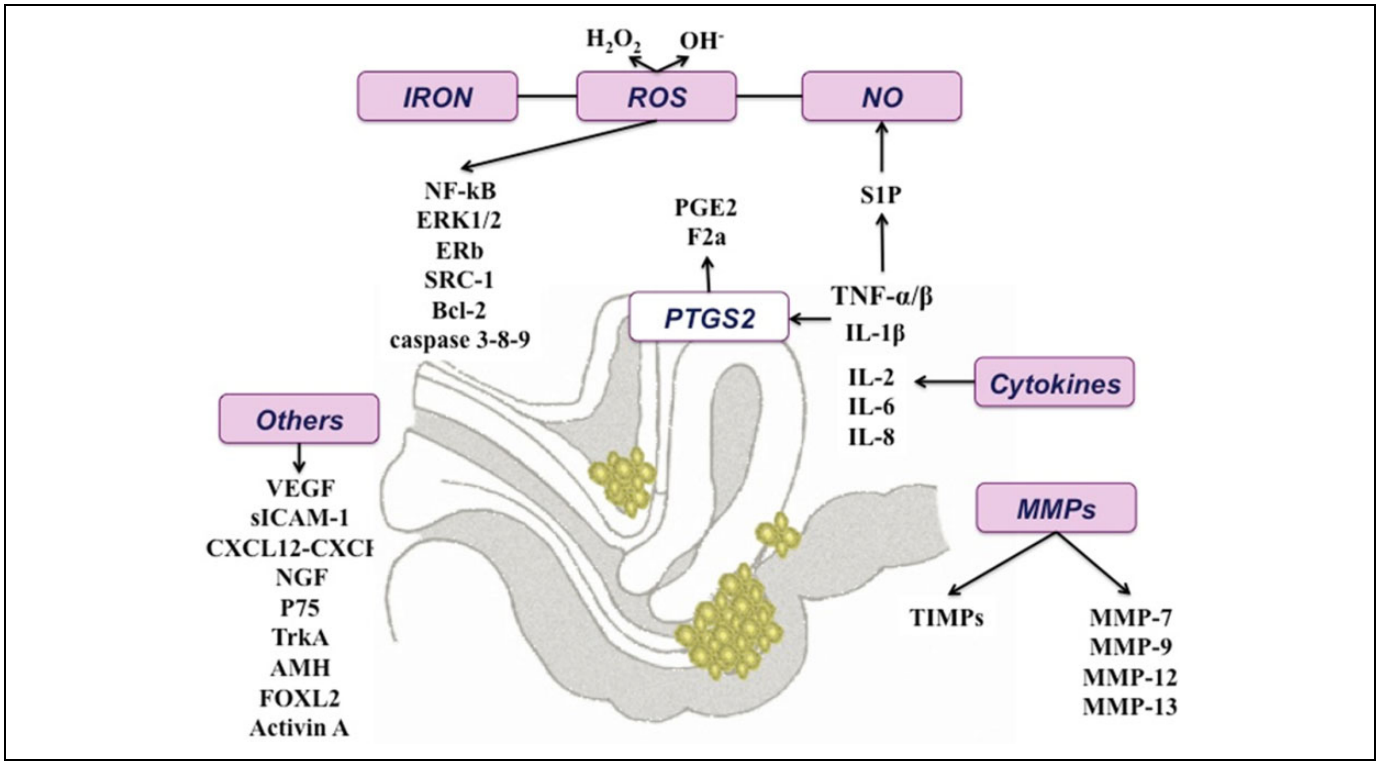

Figure 2. Molecular pathways involved in deep infiltrating endometriosis (DIE) pathogenesis.

Oxidative stress activates the ERK pathway for survival and proliferation of endometriotic cells, namely through expression of c-Fos and c-Jun, and is hyperactivated; and genes are overexpressed in a mix of patients with OMA or DIE.[39] A relationship between activation of the ERK pathway and proliferation of deep endometriotic cells is established using a specific inhibitor of phosphorylation of the protein tyrosine kinase ERK.[39] In addition to ERK pathways, an endogenous activation of the mammalian target of rapamycin (mTOR)/AKT pathways is specifically observed in cases of DIE. Using a nude mice model of endometriosis, the authors could show that Temsirolimus mTOR/AKT inhibitor prevents the development of DIE lesions (Figures 1 and 2).[40]

Oxidative stress takes place in cell proliferation and inflammation in the various forms of endometriosis and showed increased concentrations of peritoneal protein advanced oxidation protein products and nitrates/nitrites in patients with DIE compared with control women without endometriosis, correlated with multifocal intestinal DIE.[41]

Peritoneal Invasion

Therefore, when endometrial cells reach peritoneum, an upregulation of matrix metalloproteinase (MMP)-3, TGF-β, and cytokines creates a microenvironment that facilitates implantation of endometrial cells or protects them from immune-mediated clearance. The TGF-β and activin A induce endometrial cell invasion in an in vitro model of peritoneum.[42,43] Anti-Mullerian hormone (AMH) is a member of TGF-β family, and hyperexpression of AMH in lesions of DIE is also higher in OMA than in eutopic endometrium supporting a role of TGF-β in this biologic mechanism (Figure 2).[44]

The MMPs and their inhibitors (tissue inhibitors of metalloproteinases) are involved in extracellular matrix remodeling under ovarian steroid regulation; indeed the in vitro treatment with progesterone fails to fully suppress pro-MMP-7 secretion and fails to prevent the ability of the transplanted endometrium to establish experimental disease in mice.[45]

The MMP-12 polymorphism (especially the MMP-12–MMP-13 A/G–A/A combined genotype) might play a role promoting the development of peritoneal implants in endometriosis. However, the absence of association with DIE and OMA suggests MMP-12 gene, in association with MMP-13 gene, would act as a modifying gene for an unknown factor, genetic or epigenetic, and would only influence superficial endometriosis. In fact, this combination of polymorphisms seems to block the disease at the superficial stage. This specific combined genotype has been proposed as protective for the patients who will present only SPE and not OMA or DIE.[46]

Moreover, a decreased expression and enzymatic activity of MMP-9 in peritoneal macrophages isolated from patients with DIE decreases their ability to degrade basement membrane and thus its capability of phagocytosis.[47] The MMP-9 expression is also inhibited by PGE_2, which is aberrantly elevated in women with endometriosis, thus suppressing its enzymatic activity (Figures 1 and 2).[47]

Eutopic endometrial stromal cells from patients with DIE overexpress CXCR4 and are attracted by the chemokine

CXCL12, ligand of CXCR4, produced in the inflammatory peritoneal environment. The chemokine receptor CXCR4 expressed physiologically by healthy endometrium is overexpressed on eutopic endometrial stromal cells of patients with DIE. Endometriotic cells of DIE patients displayed a hyperproliferative phenotype associated with increased endogenous oxidative stress and activation of the ERK and mTOR/AKT pathways. The downregulation of CXCR4 in DIE stromal cells could be explained, as in macrophages, by intraperitoneal inflammation and hypoxia. The low expression of CXCR4 in endometriotic stromal cells could cause their arrest within the peritoneal cavity where inflammation and hypoxia are encountered. Although it is probably not the sole pathway involved, the CXCL12–CXCR4 axis probably plays a major role in the trafficking and homing of eutopic endometrial cells in the peritoneal cavity (Figure 1).[48]

Neuroangiogenesis

Endometriosis cells highly express vascular endothelial growth factor (VEGF) and this is increased in red vascular peritoneal endometriotic lesions compared to older black or white scarred lesions.[49] The angiogenic characteristics of endometriotic lesions appear to differ between SPE, OMA, and DIE. Deep endometriotic lesions of the rectum, in the stroma around the glands, have higher expressions of VEGF-A and VEGF receptor 2 and increased blood vessel density compared to samples of ovarian or bladder endometriosis or in normal ovary, bladder, and rectum. Although rectal and bladder endometrioses are examples of DIE, the vascularization and the expression of VEGF and its receptor are significantly higher in cases affecting the rectum.[2] Peritoneal red lesions, highly vascularized, exhibit a significantly increased NF-kB activation and intercellular adhesion molecule 1 expression when compared to less-active black lesions.[50] Angiogenesis is modulated by estrogen and progesterone, but locally a role is exerted by chemokines (Figures 1 and 2).

Neurogenic processes have been recently described in endometrium and endometriotic lesions contributing to explain the endometriosis-related pain mechanisms.[51,52] Local inflammatory, hormonal and angiogenetic mechanisms contribute to supporting neuronal growth.[52] Nerves frequently accompany angiogenesis (neuroangiogenesis), likely contributing to the pain associated with this disorder; nerve fibers in endometriosis implants influence dorsal root neurons within the central nervous system, increasing pain perception.[53]

Nerve fibers are present in SPE lesions,[54,55] OMA,[56] and DIE lesions.[57,58] Significantly more nerve fibers are present in SPE lesions compared to normal peritoneum.[59] Interestingly, nerve fiber density is also increased in uninvolved, microscopically normal peritoneum of women with endometriosis, even at a long distance from lesions.[54] The DIE lesions are richly innervated, with substantially greater density of nerve fibers than peritoneal lesions[57] and unaffected vaginal tissue.[59] The DIE lesions involving the bowel contain the highest densities of nerve fibers observed in endometriotic lesions.[58] Interestingly, the strongest intensity of expression of NGF and its associated receptors has been noted in DIE lesions,[57] which correlates with high patient-reported pain (Figure 2).[60]

Increased activated macrophages and degranulating mast cells in peritoneal endometriotic lesions may increase neurogenesis.[60] In fact, activated macrophages secrete neuroattractant cytokines, providing a suitable environment for nerve ingrowth.[61]

Conclusion

The underpinnings for the observed hallmarks of inflammation, estrogen dependence, and progesterone resistance in the pathophysiology of endometriosis well are established.[62] However, the disease heterogeneity is becoming a relevant clinical issue. Indeed, clinical data suggest a clear distinction in terms of diagnosis, treatment, and follow-up among OMA, SPE, and DIE.[63] Since now, most of the pathogenetic studies on endometriosis were conducted on a mix of various phenotypic manifestations.

The present review focused on the molecular studies on DIE, and more pronounced oxidative stress markers and neurooangiogenetic mechanisms were found.[64,65] With further advances in our understanding of endometriosis, preventive strategies, novel non-surgical diagnostic modalities, and targeted therapeutics hold great promise of becoming realities and help to treat our patients.[66,67]

The future research must contribute to a better phenotyping of the lesions in order to give a specific efficient management to each subgroup from OMA to DIE. Further studies with basic science approach are necessary to increase pathogenesis knowledge of endometriosis and will support DIE to be considered as a disease per se.

Declaration of Conflicting Interests

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