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REVIEW

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Endometriosis — insights into a multifaceted entity

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Abstract

Firstly described at the end of nineteenth century, endometriosis remains an enigmatic disease, from etiopathogenesis to specific markers of diagnosis and its ability to associate with malignancies. Our review has been designed from a historical perspective and steps up to an updated understanding of the disease, facilitated by relatively recent molecular and genetic progresses. Although the histopathological diagnosis is relatively simple, the therapy is difficult or ineffective. Experimental models have been extremely useful as they reproduce the human disease and allow the testing of different potential modulators or treatment options. Due to molecular resemblance to carcinogenesis, applications of anti-cancer agents are currently under scrutiny. The desired goal of an efficient therapy against symptomatic disease, along with associated infertility and malignancies, needs a deeper insight into the complex mechanisms involved in endometriosis initiation, development, and progression. Current trends in genomic and proteomic approaches are useful for a more accurate classification and for the identification of new therapeutic targets. *(Folia Histochemica et Cytobiologica 2018, Vol. 56, No. 2, 61–82)*

Key words: endometriosis; retrograde menstruation; cytokines; angiogenesis; apoptosis; precursor lesion; carcinogenesis; anti-cancer agents

Abbreviations: 5-FU — 5-fluorouracil; 8-OHdG — 8-Oxo-2'-deoxyguanosine; ACP1 — acid phosphatase 1; ALCAM/CD166 — activated leukocyte cell adhesion molecule/cluster of differentiation 166; ANXA4 — annexin A4; ARID1A — AT-rich interaction domain 1A; AKT — serine/threonine kinase or protein kinase B [PKB]; Bax — BCL-2-associated X protein; BCL-2 — B-cell lymphoma 2; bFGF — basic fibroblast growth factor; BRAF — B-raf proto-oncogene, serine/threonine kinase; BRCA — breast and ovarian cancer susceptibility protein; C — complement component; CA-125 — cancer antigen 125; CA 19-9 — cancer antigen 19/9; CAMs — cell-adhesion molecules; CETP — cholesteryl ester transfer protein; CD — cluster of differentiation; Cdk — cyclin-dependent kinase, CK — cytokeratin; CLI — chloroindazole; COX-2 — cyclooxygenase-2; CTNNB1 — catenin (cadherin-associated protein) beta 1; CYP12A1 — cytochrome P450 family 17 subfamily A member 1; DAPK1 — death-associated protein kinase 1; DNA — deoxyribonucleic acid; DRD2 — dopamine receptor D2; E2 — estradiol; EGF — epidermal growth factor; EMT — epithelial-mesenchymal transition; ENDO-I — endometriosis protein-I; ENG — endoglin; eotaxin (CCL11) — C-C motif chemokine 11; EP — prostanoid receptor (prostaglandin E receptor); ER — estrogen receptor; ERK — extracellular signal-regulated kinases; EZH2 — enhancer of zeste homolog 2; FasL — Fas ligand; FGF-9 — fibroblast growth factor 9; FGFR — fibroblast growth factor receptor; FOXP3 — forkhead box P3; FSH — follicle-stimulating hormone; Gn-RH — gonadotropin-releasing hormone; GROa (CXCL1) — chemokine

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(C-X-C motif) ligand 1; GSTM1 — glutathione S-transferase mu 1; GSTT1 — glutathione S-transferase theta 1; HER-2 — human epidermal growth factor receptor 2; HGF — hepatocyte growth factor; HIF-1α — hypoxia-inducible factor 1 alpha; sHLA-G — soluble human leukocyte antigen G; hMLH1 — human mutL homolog 1; HNF1-β — hepatocyte nuclear factor 1 homeobox B; hTERT — human telomerase reverse transcriptase; ICAM — intercellular adhesion molecule; IFN-γ — interferon gamma; Ig — immunoglobulin; IGF — insulin-like growth factor; IL — interleukin; ITGB1 — integrin beta- 1 precursor; JAK — Janus kinase; KRAS — Kirsten rat sarcoma viral oncogene homolog; LFA-1 — lymphocyte function-associated antigen 1; LH — luteinizing hormone; LOH — loss of heterozygosity; MCAM — melanoma cell adhesion molecule; MCP-1 — monocyte chemotactic protein 1; MEK — mitogen-activated protein kinase; MIF — macrophage migration inhibitory factor; miRNA — microRNA; MLH1 — human MutL homolog 1; MMP — matrix metalloproteinase; MoAb — monoclonal antibody; MSC — mesenchymal stem cell; mTOR — mechanistic target of rapamycin; MT5-MMP — membrane-type 5-MMP; MVD — microvascular density; NFκB-1 — nuclear factor of kappa light chain enhancer in B-cells; NK — natural killer; OBHS — oxabicycloheptene sulfonate; Oct-4 — octamer-binding transcription factor 4; P4 — progesterone, PAI — plasminogen activator inhibitor; PD-ECGF — platelet-derived endothelial cell growth factor; PDGF — platelet-derived growth factor; PDGFRB — platelet-derived growth factor receptor beta; PDTC — pyrrolidine dithiocarbamate; PGE2 — prostaglandin E2; PGF — placental growth factor; PGP9.5 — ubiquitin C-terminal hydrolase L1; PI3K — phosphatidylinositol 3-kinase; PI3KCA — phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PPAR-γ — peroxisome proliferator-activated receptor gamma; PR — progesterone receptor; PTEN — phosphatase and tensin homolog; PTPN22 — protein tyrosine phosphatase, non-receptor type 22; r-hTBP-1 — recombinant human tumor necrosis factor binding protein-1; RANTES (CCL5) — chemokine (C-C motif) ligand 5; SDF1 (CXCL12) — C-X-C motif chemokine ligand 12; sICAM — soluble intercellular adhesion molecule 1; SMAD — mothers against decapentaplegic homolog 1 (Drosophila); StAR — acute steroidogenic regulatory protein and aromatase; STAT — signal transducer and activator of transcription; TGF-β — transforming growth factor beta; Th — T helper cells; TIMP — tissue inhibitor of metalloproteinase; TNF-α — tumor necrosis factor alpha; TNFR — tumor necrosis factor receptor; TSG — tumor suppressor gene; TSH — thyroid-stimulating hormone; uPA — urokinase-type plasminogen activator; VEGF — vascular endothelial growth factor; VEGFR — vascular endothelial growth factor receptor; WNT4 — wnt family member 4; WT1 — wilms tumor 1; ZNF217 — zinc finger protein 217

Introduction: definition and epidemiology

The first histopathological description of endometriosis was given by Von Rokitansky, as early as 1860 [1]. By 1896, the name of "endometriomas" or "adenomyomas" had been proposed, due to the lesion resemblance to the mucous membrane of the uterus [2, 3].

Endometriosis is nowadays defined as an ectopic implantation of endometrial-like tissue, composed of both glands and stroma. Endometriosis has an incidence of about 2% in general population [4], with numerous incidental occurrences, approximately 70% of cases developing pelvic inflammatory disease, and 25–30% of cases being associated with infertility [5].

Endometriosis mainly involves the reproductive tract components (in about 75% of cases), such as ovaries, fallopian tubes, large, round, and uterosacral ligaments, uterine cervix, vagina, and recto-vaginal septum [5]. In about 25% of cases, this process may be identified in extra-reproductive organs, especially with intraperitoneal locations (peritoneum, Douglas pouch, appendix, gastro-intestinal tract, and lymph nodes) [6].

Rare extraperitoneal locations are also reported in literature, such as liver [7], lung [8], pleura or diaphragm [9], urinary tract [10], tegument, mainly post-surgical abdominal scars, *i.e.* post C-section, nasal cavity [5], iliac vein wall [11], and hernial sac wall [12].

Although it is considered a benign disease, the endometrium acquires aggressive pathological characteristics, being able to migrate, implant, proliferate, and grow in other sites than those genetically established, during endometriosis development.

Clinico-histopathological features

Endometriosis is a highly heterogeneous entity due to different degrees of clinical manifestations, with a broad spectrum, from symptomatic cases, manifested mainly with characteristic cystic lesions and adherences, to symptomatic cases although without evident lesions, and to incidentally discovered, asymptomatic cases.

Gross findings are also highly variable, from small dispersed lesions, such as superficial or "gunpowder"

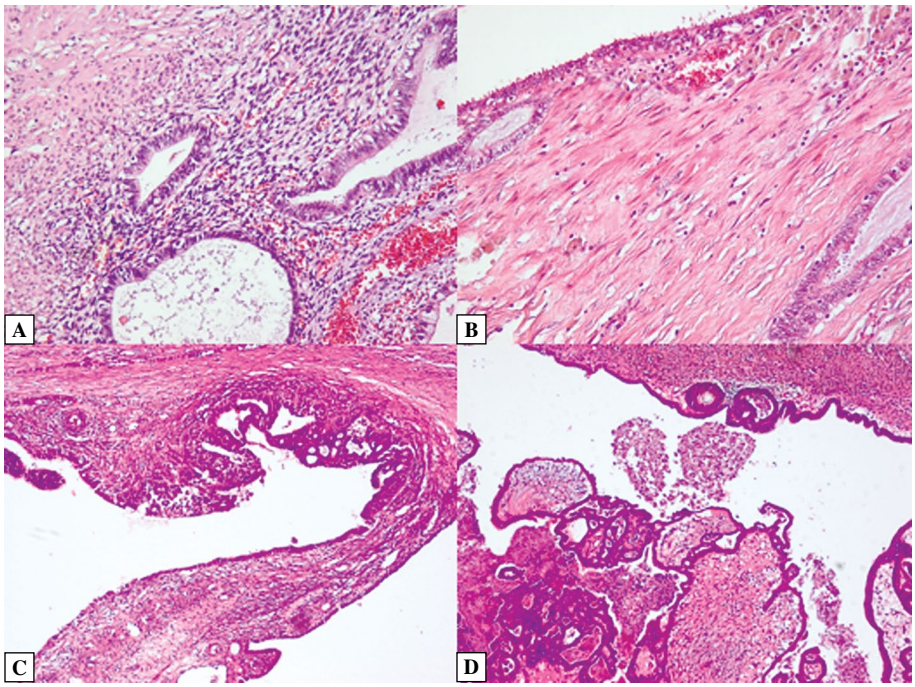

Figure 1. Distinct histological features of endometriosis. **(A)** Ovarian endometriosis containing endometrial glands and stroma in an ectopic (ovarian) location (HE, 200×). **(B)** Ovarian endometriosis with evident hemosiderin-laden macrophages (HE, 200×). **(C)** Ovarian endometriosis associated with an area of atypical endometriosis, with a complex architecture (HE, 40×). **(D)** Ovarian endometriosis (upper field) associated with endometrioid carcinoma (inferior) (HE, 40×).

appearance, to cystic, red implants, or petechiae, vesicles, nodules, and, sometimes, polyps, depending on their location, duration, and association with fibrous adhesions [13].

A combined anatomical and histopathological classification recognizes three main types of endometriosis: endometrioma, peritoneal, and deep infiltrative lesions [9].

Endometrial cysts or endometriomas usually involve the ovaries, exhibit bilateral location in around one third of cases and develop until almost completely replacing the ovarian parenchyma [13]. They are most commonly associated with fibrous walls, adherences to neighboring structures, and usually chocolate-colored inspissated or semifluid content [13]. If larger than 15 cm in diameter or associated with polypoid projections or solid areas, a developing neoplasm should be considered [13].

Peritoneal endometriosis may involve (in decreasing order of frequency): ovaries (30%), uterosacral and large ligaments (18–24%), fallopian tubes (20%), pelvic peritoneum, Douglas pouch, and gastro-intestinal tract [5, 6].

Deep infiltrative endometriosis has been identified in 30–40% of patients diagnosed with endometriosis [5], involving pelvis and gastrointestinal tract [6].

Histopathological findings have been based on the identification of endometrial glands surrounded by characteristic cellular stroma (Fig. 1A), registering an analogous pattern to the eutopic endometrial cycle.

Although histopathological diagnosis can be relatively simply reached, the microscopic differentials with ovarian endosalpingiosis [13], a lesion frequently overdiagnosed as endometriosis, has to be made. This may be achieved by the identification of a stromal inflammatory infiltrate, containing variable amount of lymphocytes, a reduced number of other inflammatory cells, with evident hemosiderin-laden macrophages (Fig. 1B), as proof of a cyclic evolution of the ectopic tissue, although a ceroid pigment may occasionally confer a pseudoxanthoma appearance to these cells [13]. Rarely, benign cystic lesions or even well differentiated adenocarcinomas may be included in the differential diagnosis. Currently, immunohistochemical profile may be useful, by CD10 strong stromal positivity, ERβ and PR-A variable epithelial and stromal positivity, along with Bcl-2 and Ki-67 epithelial and stromal positivity correlated to the size of the implant, supplementing the histological characteristics exhibited in routine staining [14].

The accumulation of data on endometriosis has been facilitated by comparative studies between native and experimental disease, due to a close resemblance of both laparoscopic findings and microscopic patterns demonstrated between animal models and their corresponding human disease [15].

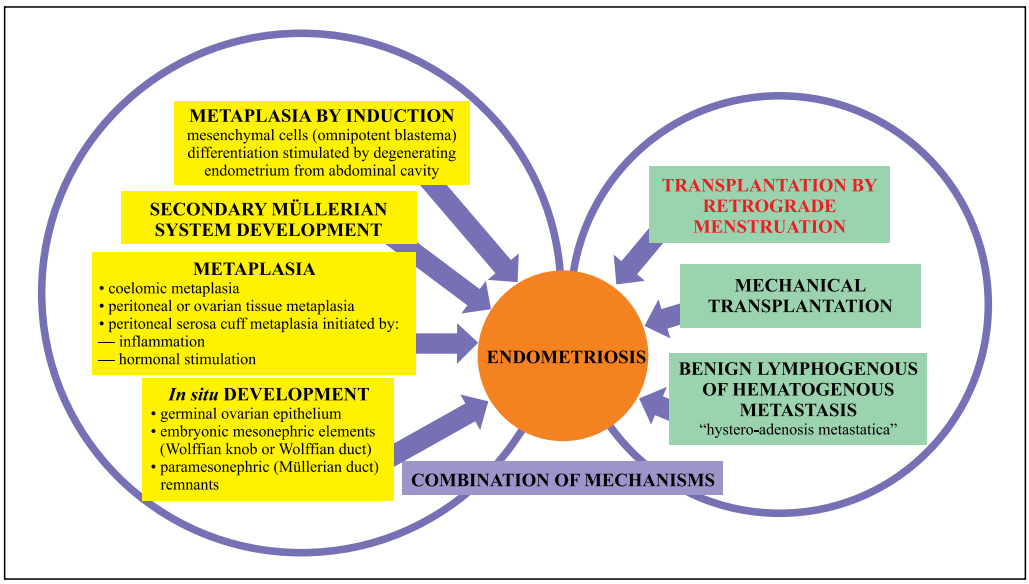

Figure 2. Etiopathogenic theories of endometriosis: from past to current concepts and combination of theories. Detailed description in the main text.

Markers for diagnosis

The specific markers of endometriosis may be classified into three main categories (Table 1): (i) peritoneal and/or serum, (ii) endometrial and biochemical-endometrial, and (iii) genetic types.

Peritoneal and/or serum markers are grouped into several categories, as follows: glycoproteins [16–19], growth factors [18, 20–27], proteolytic enzymes and their specific inhibitors [28–32], soluble adhesion molecules [33–37], hormones [38–43], cytokines [42, 44–57], autoantibodies [58, 59], and environmental contaminants [60]. The diagnostic value of some of these markers has been quantified and, as a result, two peritoneal and/or serum cytokines may be useful in the diagnosis of endometriosis, such as increased serum IL-6 (threshold of 2 pg/ml) [49], and serum or peritoneal fluid TNF-α (threshold of 15 pg/ml) [49], although conflicting results are reported in possible correlation with disease stage, location, endometrial cycle phase, control groups, and assay type [49].

The endometrial and biochemical-endometrial markers are considered as stromal [61, 62], glandular [62–64], neuronal [65], proteolytic enzymes and their specific inhibitors [28–31, 66–70], adhesion molecules [34, 62, 71–74], osteopontin [75], hormonal receptors [38, 39, 76–80], and mesenchymal stem cells [81–85].

Genetic markers belong to variable categories, such as: oxidative stress genes [86], tumor suppressor genes [87–98], oncogenes [90, 99–103], regulatory genes [104, 105], DNA repair genes [93], chromosomal aberrations or amplifications [106–108], loss of heterozygosity [87, 107, 109], genetic polymorphism of variable genes [107, 110–119], and genome-wide alterations [120, 121].

The prospective clinical validation of these markers and determination of their clinical utility may lead to the development of a successful commercial test for endometriosis diagnosis.

Past to rediscovered etiopathogenic theories and recent contributions

Short overview — historical hallmarks

Endometriosis is considered as the "theories disease", taking into account numerous past and modern etiopathogenic hypotheses which have been launched during a long period of attempts to explain its nature [4, 9] (Fig. 2).

According to the past theories, endometriosis may result by *in situ* development from germinal ovarian epithelium [122], from embryonic mesonephric elements (Wolffian knob and Wolffian duct) [9], or from paramesonephric (Müllerian ducts) remnants [3, 9, 123].

Other hypotheses are those of metaplastic processes, as coelomic metaplasia [9, 124–126], or metaplasia of the peritoneal or ovarian tissue [127, 128], or metaplasia of the peritoneal serosa cuff initiated by inflammation [9, 129] or by hormonal stimulation [130]. The possibility of metaplasia development, by differentiation of mesenchymal cells (omnipotent blastema) activated by substances released by degenerating endometrium eliminated into the abdominal cavity, has been also proposed [131, 132].

Table 1. Spectrum of markers in endometriosis diagnosis and follow-up

Peritoneal and/or serum markers	Endometrial markers	Genetic markers
Glycoproteins CA-125 [16–19], CA 19-9 [18]	**Stromal** CD10 [61], Vimentin [62]	**Oxidative stress** 8-OHdG, [86]
Growth factors EGF(R) [20], TGF-β [21], SF/HGF [22] FGF-9 [23], VEGF [20, 24], Angiopoietins [25], Glycodelin [26, 27]	**Glandular** CK18 [62] Glycodelin [63, 64]	**Tumor suppressor genes** PTEN [87–89], P53 [90, 91], P16 [92, 93], ARID1A [94–96], WT1 [97], DAPK1 [98]
	Neuronal PGP9.5 [65]	**Apoptosis** Bcl-2 (anti-apoptotic) [90, 99, 100] Survivin (anti-apoptotic) [101]
		Oncogenes HNF1-β [102], KRAS [103]
Proteolytic enzymes and their specific inhibitors MMPs/TIMPs [28–31] Cathepsin D [32]	**Proteolytic enzymes and their specific inhibitors** MMPs/TIMPs [28–31, 66–69] plasminogen activators / plasminogen activator inhibitors [70]	**Regulatory genes** PIK3CA, FGFR [104, 105]
		DNA repair hMLH1 [93]
		Chromosomal aberrations aneusomies (chrs. 1, 7, 9, and 17) [106, 107]
Soluble adhesion molecules E-cadherin, P-cadherin, β-catenin [33,34] ICAM-1 [35] sHLA-G [36] Osteopontin [37]	**Cell adhesion molecules** E-cadherin, P-cadherin, CD44 [34, 62, 71–74]	**Chromosome amplification** 20q13.2, 12p12.1, 17q12, 9p21 [108]
	Osteopontin [75]	**Loss of heterozygosity** 4q, 5q, 6q, 9p, 11q, 22q, 10q23.3, 17p13.1 [87,107,109]
Hormones E2, P4 [38, 39] FSH, LH, TSH [40] Leptin [41–43]	**Hormonal receptors** ER-β, ER-β:ER-α [38, 39, 76, 77] PR-A [78] FSHR, LHR [79, 80]	**Genetic polymorphism candidate genes** TP53 (17p13) [107] VEGF (6p21-12) [110] ACP1 (2p25) [111] PTPN22 (1q13) [112] DRD2 (11q32) [113] FOXP3 (Xp11.23) [114] GSTM1 (1p13) [115] GSTT1 (22q11) [115] IL-10 (1q31-32) [116] CETP (16q21) [117] TNF-A (6p21) [118] CYP17A1 (10q24) [119]
Cytokines IL-1B, IL-4, IL-6, IL-8 (CXCL8) IL-10, IL-12, IL-17A, IL-18, IL-22 [44–51] MCP-1 (CCL2) [52] RANTES (CCL5) [53], GRO-α (CXCL1) [47], SDF1 (CXCL12) [54, 55], MIF [56, 57]	**Mesenchymal stem cells** Oct-4 [82] Htert, Musashi-1 [84] CD73 MSC/migration (NT5E) [83] CD90 MSC/marker of T cells (THY-1) [81,83,85] CD105 MSC (ENG) [83, 85] CD140B (PDGFRB) [81] CD146 (MCAM) [81] CD29 MSC/adhesion molecule (ITGB1) [81] CD44 MSC/hyaluronic acid receptor [81, 83] CD9 MSC/angiogenesis [83] CD41a MSC/fibrinogen receptor [83] ALCAM/CD166 [85]	**Genome-wide** VEGFR-2 (4q11-q12) [120] WNT4 (1p36.12) [121]
Autoantibodies IgG anti-laminin-1 [58] anti-endometrial [59]		
Environment contaminants dioxin-like chemicals [60]		

A secondary Müllerian system development is suggested by another theory launched in 70s [128].

As a result of further studies and epidemiologic characteristics, the hypothesis of transplantation, due to retrograde menstruation [9, 133, 134], or to mechanical transplantation [9] has been later developed.

In order to find a possible mechanism for implants' development in other locations which could not be ex-

plained by previous hypotheses, benign lymphogenous or hematogenous metastasis (hystero-adenosis metastatica) [135, 136], or combinations of *in situ* development with endometrial transplantation and implantation or induction theory [132, 137] have been later proposed.

Mechanisms and dynamics of endometriosis: current concepts

Considering the wide distribution of endometriosis locations within human organism, modern theories try to combine the effect of multiple contributors, as multi-factorial, multi-compartmental pathogenic phenomena, associated with epiphenomena, as sequelae of the primary lesions, such as estrogen dependence [138], genetic susceptibility [139], and the possibility of direct spread by "transplantation" [9]. These processes are added to the incapacity of the immune system to neutralize ectopic endometrial cells [140–142], or the contextual environmental factors to intervene in the process, and the occurrence of congenital defects, such as atretic hymen. The last but not the least, the most plausible pathogenic mechanism is the involvement of stem cells as the main "culprits" in the process of ectopic implantation *via* retrograde menses.

Retrograde menstruation and stem cells: a new perspective of an old theory

The currently agreed endometriosis pathogenic mechanism is that of retrograde menstruation, *via* fallopian tubes, a theory that had been launched by Sampson, as early as in 20's. There are numerous elements that plead for the accuracy of this theory, as following: the retrograde menstruation is quite frequent, being estimated that viable endometrial cells may be found in peritoneal cavity in about 76–90% of women, in non-menstrual periods of time or in peritoneum, during menstruation or immediately after this phase [143]. Furthermore, the blocking of evacuation of the menstrual blood results in extended endometriosis [143]. Moreover, an endometriosis onset at prepuberty is quite rare [143].

The counterarguments of the involvement of this mechanism are provided by evidences that endometriosis may appear in areas which are inaccessible to menstrual reflux, including extra-peritoneal locations, a finding that may support lymphatic or hematogenous cells migration [4].

Relatively recent data have demonstrated the occurrence of mesenchymal stem cells and progenitor endometrial cells in endometriosis and their possible evolution toward differentiation into nine cellular lines: adipocytic, osteogenic, cardiomyocytic, respiratory epithelium, neurocytic, myocytic, endothelial, pancreatic, and hepatic types [144].

Although a key role is attributed to the stem cells reflux into the peritoneal cavity, the microenvironment factors that stimulate stem cells' functions and allow the development of endometriotic implants are very important in the retrograde menstruation mechanism.

Role of metalloproteinases

MMPs are involved in endometrial turnover and its pathology [145]. In endometriosis, after the attachment to the ectopic sites, the epithelial endometrial cells invade the extracellular matrix. It has been demonstrated that this process occurs with the involvement of MMPs, their high concentration in the peritoneal fluid being stimulated by TNF-α and IL-1 [146]. Concomitantly, TNF-α inhibits TIMP-1 and TIMP-2 [147], resulting in an unbalanced MMPs/ /TIMPs ratio [17, 18, 28, 30, 31]. Increased MT5-MMP expression [31] and alterations of the balances between MMP-9/TIMP-1 [30], MMP-9/TIMP-3 [28], MMP-3/uPA [66], VEGF/MMP-3/uPA [68], VEGF/ /MMP-2/CD44/Ki67 [69], PAI/TIMP-1 [70], and IL-1/ /MMP-1 [67] are characteristic features of endometriosis (Table 1).

Inflammation: cells and cytokines

Another important feature in endometriosis pathogenesis is attributed to the occurrence of pelvic inflammation. Numerous studies have demonstrated that macrophages, lymphocytes, endometrial and mesothelial cells are capable of producing cytokines and inflammatory mediators such as ILs [45–51, 67, 148], TNF-α [149, 150], PGF2, PGE2 and thromboxane B2 [151], MCP-1 [52, 152], RANTES [53], eotaxin [153], GROa [47], SDF1 [54, 55], and MIF [56, 57, 152, 154, 155]. These cytokines recruit numerous cellular types, such as macrophages, lymphocytes, eosinophils, mast cells, and endometrial cells into the peritoneal cavity. This process is followed by cascade of events leading to the stimulation of endometriotic cells proliferation, along with their adhesion to ectopic substrates, angiogenesis, and stimulation of the release of other cytokines and chemokines, furthermore amplifying their effects.

Peritoneal macrophages seem to have the highest capability of secreting various types of cytokines and inflammatory mediators. Macrophages amplify the activity of COX-2 and PGE2, which results in VEGF stimulation in endothelial cells of endometriotic implants, together with that of StAR, resulting in an increased estrogen level in the endometrial tissue [23, 156–160]. Estrogens and PGE2 are inducing FGF-9 expression that activates endometrial cells proliferation, in a parallel manner to the stimulation

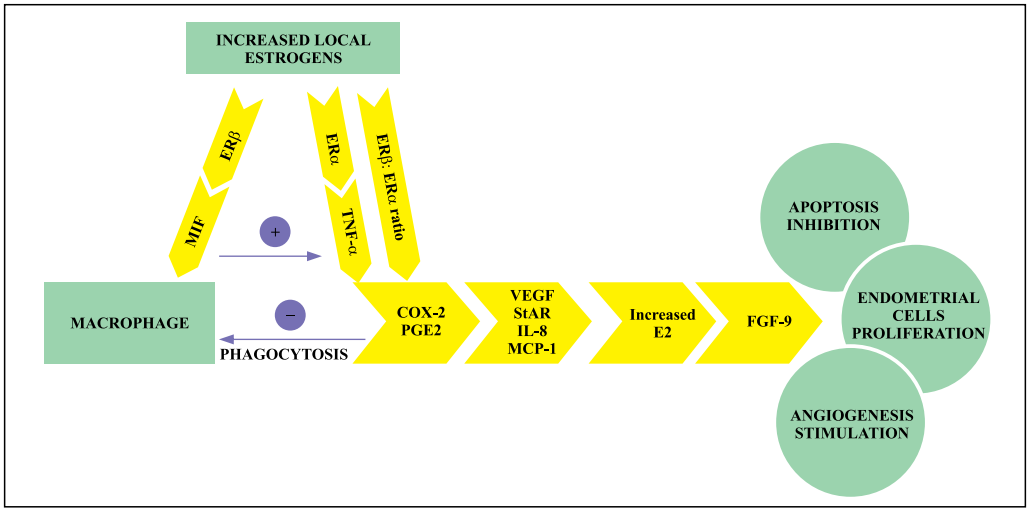

Figure 3. Pivotal role of macrophages in the development of endometriosis results from amplifying the activity of COX-2 and PGE2 production, stimulation of VEGF, StAR, IL-8 and MCP-1 secretion, increased estradiol (E2) level and FGF-9 synthesis, which leads to endometrial cells proliferation, stimulation of angiogenesis, and apoptosis inhibition. MIF, induced by local estrogen reciprocally stimulates TNF-α in endometrial cells. PEG2 acts as an inhibitor of phagocytosis. Furthermore, altered ER expression of estrogen receptors (ER) stimulates the cascade of events. Detailed description in the main text.

of angiogenesis and apoptosis inhibition [23]. PGE2 suppresses the activity of phagocytes, allowing the development of endometriotic implants [23] (Fig. 3).

NK cells have been also incriminated in endometriosis pathogenesis. The hypothesis of an inefficient clearance of the endometrial cells from the peritoneal cavity has been proposed [161, 162], due to peripheral and peritoneal NK cells failure to eliminate autologous dendritic cells [163] expressing self-endometrial antigens what results in their presentation to autoreactive T cells and the production of auto-antibodies [164].

Lymphocytes are also involved in various cytokines production with potential role in endometriosis development. Peritoneal fluid Th2 cells were shown to stimulate the secretion of IL-4 and IL-10, mainly by peritoneal macrophages, resulting in an aberrant suppression of cell-mediated immunity what may enable implantation of endometrial cells in peritoneum [165].

Moreover, the NK cell-mediated cytotoxicity, manifested by lymphocytes adherence to endometrial cells by LFA-1 — ICAM-1 pathway and their presentation as targets to NK cells, may fail in endometriosis. This finding has been demonstrated by an *in vitro* study [166] and later on confirmed by flow cytometry in human endometriosis [167]. According to this possible mechanism involved in endometriosis pathogenesis, sICAM-1 may bind to LFA-1 expressing lymphocytes, preventing endometrial cells recognition by lymphocytes and, furthermore, preventing NK-mediated cytotoxicity [166]. Consequently, endometriosis is characterized by the inability of immune cells to send death signals to endometrial cells and/or the ability of ectopic endometrial fragments to avoid cellular death due to an increased expression of anti-apoptotic molecules [168].

TNF-α, a pro-inflammatory cytokine, is also produced by macrophages, exhibiting elevated levels in the peritoneal fluid [36, 169] and serum [169] in endometriosis patients. It has been shown recently that TNF-α-induced IKKβ complex activation leads to the initiation and progression of endometriosis, by enhancing the viability of the ectopic epithelial cells but not eutopic epithelial cells, or endometrial stromal cells [170].

MIF, another cytokine, shows a high level in the peritoneal fluid, in circulation, and in peritoneal macrophages, its secretion being induced in endometriosis by estrogens [171]. MIF stimulates endothelial cell proliferation, endometriotic lesion survival, expression of PGE2, COX-2, VEGF, IL-8, MCP-1, aromatase, and reciprocally stimulates TNF-α in endometrial cells [56, 152, 158, 172]. ISO-1, MIF antagonist, is responsible for a significant reduction in endometriotic lesion size, in experimental models, by inhibiting cell adhesion, tissue remodeling, angiogenesis, and inflammation, in addition to alteration of the balance between pro- and anti-apoptotic factors [155].

Hormones and hormone-like substances in the pathogenesis of endometriosis

Steroid hormones play an important role in endometrial physiology and their unbalanced activity is involved in endometrial pathology, including endometriosis.

In this regard, it has been demonstrated that the driving factor of the production of cytokines in endometriosis is the altered responsiveness to progesterone, showing a characteristic very low expression of progesterone receptor A (PR-A) and the absence of PR-B in mice models [173], and in a similar way with decreased PR-B/A ratio and reduced PR-B immunoreactivity, demonstrated in human endometriosis [78, 174].

Supplementary, the increased local estrogen levels further drive the endometriotic lesion phenotype and increased cytokine expression and apoptosis in a murine endometrium [175]. Hormonal dependence in endometriosis is demonstrated by an increased ER-β expression (approximately 100 times more than that of eutopic endometrium), due to altered methylation in the *ESR2* gene promoter [174]. ER-β overexpression suppresses ER-α expression and, furthermore, leads to an abnormally high ER-β/ER-α ratio, which is responsible to a reduced expression of PR and an increased COX-2 expression [38, 39, 77, 171]. ER-β activation results in the stimulation of MIF expression and production in the cultures of human endometrial cells [171]. In experimental endometriosis model, ER-β seems to be responsible for the inhibition of endometriotic cell apoptosis and the increased cytokine production, such as MCP-5, IL-1β, and IL-16, which results in enhanced cell adhesion and proliferation [175].

Stimulation of COX-2 activity by MIF results in the increased secretion of PGE2 that is considered a master regulator of endometriosis on the basis of its pro-inflammatory actions documented by its elevated levels in human endometriotic tissue and in peritoneal fluid [158, 176].

Angiogenesis in endometrial tissue

The angiogenic activity is stimulated in endometriosis by a large spectrum of angiogenic factors such as IL-1 [177], IL-6, IL-8, VEGF [178], ENDO-I (an endometrial haptoglobin homologue) [179], angiogenin [180], pleiotrophin, midkine [181], TNF-α [182], PGF [183], angiopoietin [25], and glycodelin [26, 27]. Moreover, in endometriosis the physiological angiogenic activity is supplemented by the co-existence of pathologic angiogenesis, immune suppression, and immune activation [184]. Environmental factors, such as dioxins, may be also responsible for an increased angiogenesis [60].

VEGF-A role is demonstrated by its increased concentrations in serum, peritoneal fluid, and endometrium of patients with endometriosis [17, 185, 186]. For instance, it was found that high levels of serum VEGF-A are useful for the diagnosis and follow-up in advanced stage of endometriosis [17]. Moreover, it was confirmed that the expression of *VEGF-A* gene was higher in peritoneal endometriosis compared with normal peritoneum [185].

One of the tools to assess angiogenesis in endometriosis is the measurement of vascular surface density (microvessel density or mean vascular density, MVD) [187]. An *in vivo* study, using transvaginal color and power Doppler, has demonstrated the correlation between high MVD and pelvic pain in patients with endometriosis [188]. This finding has been validated by immunohistochemical evaluation of CD34-labeled vessels [24, 188]. Although the active lesions showed a high mitotic index and increased MVD in implants, no significantly increased VEGF expression has been found, suggesting the involvement of other angiogenic factors [24].

Apoptosis

An apoptosis evasion mechanism has been demonstrated in endometriosis, allowing the development of ectopic implants. This particular mechanism has been characterized by increased expression of anti-apoptotic Bcl-2 along with decreased pro-apoptotic Bax expression [99, 100]. Apoptosis may be also regulated by Fas ligand (FasL) by its binding to cell membrane receptor, Fas. FasL binding results in extrinsic (autocrine or paracrine) induction of apoptosis [189]. It was found that in cultured human endometrial stromal cells IL-8 up-regulated FasL protein expression and decreased apoptosis rate [189], the latter found in human endometrial tissue was associated with increased mRNA levels of survivin and MMPs [101].

Multistep development of endometriosis

The results of numerous studies in humans and in animal models allowed proposing a multistep etiopathogenic mechanism of endometriosis [50, 190–197].

Following retrograde menstruation which is the triggering phenomena responsible for an increased number of endometrial cells in peritoneal fluid, other associated mechanisms are contributing to immune surveillance failure (*i.e.* decreased NK cytolytic [46] and cytotoxic [162, 198] activity, ICAM-1 secretion [35]), that is further supplemented by decreased apoptosis of endometriotic cells [175, 199]. The next stage is marked by the localization of refluxed endometrial cells in the peritoneal cavity, followed by increased number of activated macrophages, increased secretion

of proinflammatory cytokines, such as IL-1β, IL-6, IL-8, IL-12, IL-17A, IL-18, IL-22 [44–52] and TNF-α [42, 146, 170], chemokines (*e.g.* MCP-1 [42, 52] and RANTES [53, 200]), and growth factors, such as EGF, FGF-9, TGF-β, and HGF [20–23]. The following step is the adherence of ectopic endometrium, followed by implantation and invasion, being associated with the stimulation of TGF-β, IL-1, TNF-α, along with MMPs and TIMPs secretion [28–31, 42, 50, 201, 202].

After the ectopic implantation and invasion, other processes take place: stimulation of angiogenesis due to enhanced levels of IL-1, IL-6, and VEGF, decreased immune surveillance, increased presentation of self-antigens by dendritic cells, T and B cells activation, elevated levels of autoantibodies, and positive feedback enhancing inflammation and immune responses [141].

These cascading events are responsible by the continuous development and persistence of endometriosis. The available evidence strongly suggests that pivotal factors can be attributed to cytokines and growth factors produced by activated macrophages which not only fail to eliminate but promote development of endometriosis.

Endometriosis versus carcinogenesis

Relationships between endometriosis and malignancy

As early as in 1927, the idea linking endometriosis with malignant transformation has been hypothesized [203], mainly for the ovarian location. Since then, numerous studies have demonstrated the overlap of definition criteria of malignant phenotype with those of endometriosis. Results of meta-analyses revealed their increased association [204, 205].

Clinicopathological, molecular, and genetic evidences support the hypothesis of endometriosis as a neoplastic process, with a potential to malignant transformation. The first evidence is that of the common features shared by these entities that are both able to disseminate, to invade, and to form distant implants [206]. Moreover, a significant association of endometriosis with clear cell and endometrioid ovarian carcinomas has been reported [87, 95, 103, 104, 106, 207–211], *e.g.* 30–55% and 30–40%, respectively [206]. Furthermore, an increased incidence of concurrent primary malignancy, *i.e.* endometrial carcinoma, in endometriosis-associated ovarian malignancies suggests common molecular pathways in both locations [212]. A plethora of phenomena are common in sporadic cancer and endometriosis, being determined by complex interactions between hereditary polygenic alleles of low penetrance (polymorphism), acquired genetic alterations, leading to a "signature" of mutations, and microenvironment "permissive" factors, expressed by hormonal influences and chronic inflammation [44, 210, 212]. The current molecular techniques of genetic, transcriptomic and proteomic profiling allow for better characterization of correlations between genetic and local *milieu* alterations and transition process from normal endometrium to malignant transformation.

A large spectrum of tumors and tumor-like conditions associated with endometriosis has been described, such as polypoid endometriosis, benign tumors (such as endometrioid adenoma, adenofibroma, cystadenofibroma, and cystadenoma), premalignant changes (*i.e.* atypical endometriosis) (Fig. 1C), borderline tumors (*e.g.* endometrioid cystic adenofibroma and endometrioid cystadenofibroma), and malignant tumors, such as endometrioid adenocarcinoma (Fig. 1D), with squamous elements or with clear cell elements, low-grade and high-grade stromal sarcoma, and malignant tumors with mixed components (*i.e.* adenosarcoma and carcinosarcoma) [109, 206, 212–215].

Another criterion in favor of a relationship between endometriosis and malignancies is that endometriosis consists of a monoclonal tissue development, acquiring many of the cellular characteristics of malignant transformation [4]. Furthermore, the analysis of common features of endometriosis and tumors has revealed that endometriosis can be regarded as an estrogen-dependent neoplasm with an estrogen-induced signaling mechanism characterized by increased production of estrogens [38, 39], increased P450 cytochrome aromatase activity [171], increased activity of StAR [156], increased PGE2 production [156, 158], increased estrogen responsivity by ER-β overexpression, decreased ER-α expression and abnormal high ER-β: ER-α ratio [76, 77], decreased expression and responsivity of PR [78], and hereditary genetic polymorphism of drug-metabolizing enzymes [216, 217].

It is also widely recognized that in both endometriosis and cancer, there is co-existence of pathologic angiogenesis [218]. Importantly, an increased MMPs expression associated to deregulation of the intercellular adherence signaling is identified both in endometriosis pathogeny and in carcinogenesis.

The current knowledge is that two pathways seem to be involved in endometriosis and its potential progression toward neoplasia: either malignant transformation, probably by an atypical transition stage, either the common precursor mechanism or predisposing factors are shared by both processes, with a consecutive molecular divergence [219]. Relatively

recent histopathological data confirm the possibility of transition due to identification of an atypical stage and frequent association of ovarian cancer to atypical endometriosis. The significance of borderline tumors is currently regarded as a part of endometriosis-associated ovarian carcinoma spectrum [206, 214, 215]. Moreover, recent evidences indicate that patients with endometriosis have a significant risk for endometrial cancer, mainly endometrioid and clear cell subtypes [220].

Endometriosis as a precursor lesion

In endometriosis pathogenesis, an important role has to be attributed to polygenic susceptibility, which implies a metabolic, endocrine, and immune associations, responsible for the increase of the number of endometrial cells and/or immune surveillance decrease and by specific qualities of endometrial cells from the peritoneal fluid and/or pelvic inflammation [221–223]. Furthermore, the progressive accumulations of genetic alterations of tumor-suppressing genes and oncogenes are probably responsible for endometriosis development and its possible association with the development of malignancies [87–89, 92, 107, 224, 225].

In numerous studies it was shown that the genetic polymorphism is predisposing either to endometriosis (*e.g.* of *ICAM-1* or gene promoters of IL-6 and IL-10), or to cancer (of genes encoding IL-6, IL-8, TNF-α, NFκB-1, and PPAR-γ) [52, 216, 225, 226]. Moreover, the processes involved in endometriosis development are supplemented by genomic instability which contributes to the transition to the stage of atypical endometriosis. Mutations of genes linked to carcinogenesis have been also identified in endometriosis, such as alterations of tumor suppression genes [87–98], inactivation of DNA mismatch repair genes, by hypermethylation [93], and LOH [87, 107, 109, 219]. Thus, the next step represented by a transition or pre-malignant phase, is characterized by 4q, 5q, 6q, 9p, 11q, 22q, 10q23.3, 17p13.1 LOH [87, 107, 109, 219], inactivating mutation of PTEN [87–89, 93, 227, 228], loss of TP53 [90, 91, 107, 228, 229], mutations located at multiple loci of beta-catenin, and cadherin switch [34, 71, 73, 104], contributing to the development of endometrioid and clear cell ovarian carcinoma [227–229]. Furthermore, somatic mutations in TSG germinal lines may add support to this hypothesis [107, 224, 225].

Considering the panel of genetic mechanisms which act synergistically contributing to cancer genomic instability, with variable overlapping contribution, such as oncogenic activity, TSG inactivation, DNA repairing enzymes anomalies, inactivation of checkpoints genes of cellular cycle assembly, and telomere dysfunctions, some of these pathways have to be also detected in precursor lesions. As expected, premalignant lesions (atypical endometriosis) are characterized by several mutations of tumor suppressor genes, oncogenes, CAMs, and furthermore LOH and inflammatory immunomodulation [198]. Table 2 summarizes the arguments in favor of a common genotype in endometriosis and endometriosis-associated ovarian cancers.

Novel approaches and therapeutic agents in endometriosis

Acknowledging the role of hormonal stimulation in endometriosis, a panel of drugs has been developed to modulate the excessive ovarian estrogens synthesis, *e.g.* oral contraceptives (containing an estrogen component, such as ethinyloestradiol, mestranol, estradiol or its pro-drug estradiol valerate, combined with a progestogen, such as levonorgestrel, norethisterone, drospirenone, gestodene, desogestrel, nomegestrol, dienogest or cyproterone) [248], gestagens [249], and danazol ((17a)-Pregna-2,4-dien-20-yno[2,3-d] isoxazol-17-ol) [19]. Danazol has hormonal action, by antigonadotropic action, androgenic activity, and interaction with ERs and is also considered a powerful immunologic tool in endometriosis, due to its ability to decrease immunoglobulins, C3 and C4 complement, auto-antibodies against phospholipid antigens, and CA-125 levels, as well as its capacity to suppress lymphocyte proliferation, along with suppression of IL-1 and TNF-α production by macrophages [19].

The analysis of the common characteristics of carcinogenesis and endometriosis development, such as sustained proliferative capacity, evasion of growth suppressors and of immune destruction, replicative immortality, involvement of tumor-promoting inflammation, angiogenesis, invasion and metastasis, genome instability and mutations, resistance to cell death stimuli, and deregulation of cellular energetics, lead to the enlargement of the therapeutic arsenal by targeting common molecules and molecular pathways involved in endometriosis and endometriosis-related ovarian cancers [96, 102, 208, 230, 250–256].

Thus, by comparing the similar molecular pathways identified in both endometriosis and other cancers (*i.e.* breast, ovary, and endometrium cancers), a series of anti-cancer agents are currently in different clinical trials for endometriosis therapy, awaiting their validation. Table 3 documents the progress achieved in endometriosis by therapy with anti-cancer agents [102, 201, 208, 230–233, 250–259]. Novel therapeutic approaches applicable in endometriosis show at least five categories of anti-cancer agents that may relate

Table 2. Common molecular features in endometriosis and ovarian cancer

Role	Pathway/Molecule	Endometriosis	Endometriosis — associated ovarian cancers
Tumor suppressor	ARID1A ± BAF250a mutation [94, 95, 96, 105, 209, 230–233]	expressed [105, 233]	expressed [94, 95, 96, 105, 209, 230–232]
	PTEN somatic mutations [87–89, 93, 227, 228, 234]	expressed [88, 89, 93, 227, 228]	expressed [87, 88, 227, 228, 234]
	PIK3CA mutations [96, 104, 207]	early event in endometriosis transformation [104]	expressed [96, 104, 207]
	TP53 [90–92, 107, 213, 228, 229]	expressed (late stages) [91, 92, 107, 228]	expressed (advanced stages) [90, 213, 228, 229]
Oncogene	KRAS ±BRAF [103, 235]	expressed (atypical endometriosis) [103, 235]	expressed (mucinous type) [103]
	CTNNB1/WNT/β-catenin [72, 227, 236, 237]	expressed (atypical endometriosis) [72, 237]	expressed [227, 236]
miRNA profiling	miRNA instability [238–244]	miR-9 [238–244]	absent [238]
Microsatellite instability	BRCA1/2 [245]	absent –	expressed [245]
LOH	9p, 11q, 22q [246]	expressed [246]	absent –
	10q23 [109]	expressed (atypical endometriosis) [109]	expressed [109]
Immunomodulation	complement pathways [247]	expressed [247]	expressed [247]

their main action to hormonal substrate, angiogenesis, apoptosis, cellular cycle, and immune status.

Hormonal status is addressed by administration of aromatase inhibitors (letrozole, anastrozole) which block the conversion of androstendione to estrone, creating a low estrogen environment [260]. Another approach is to modulate ER activity, either by ER-β ligands (CLI or OBHS) already used in clinical practice [261] or by selective ER modulators (arzoxifene, bazedoxifene [262], raloxifene [263]) which are still tested in experimental models. In the regulation of progesterone action, P4 antagonists (mifepristone, RU-486 [264]) and selective PR modulators (asoprisnil, BAY 1002670) [265], PF-02413873 [266]) have shown promising results in endometriosis therapy in either clinical application or in rodent experiments. In order to eliminate the systemic side effects, Mirena coil (levonorgestrel-releasing intrauterine system) has been added to the therapy [267]. In an attempt to regulate the hypothalamic stimulation of the hormonal axis, Gn-RH agonists (elagolix [268], leuprolide, nafarelin, buserelin, goserelin, triptorelin [269], abarelix [270]) showed regression of human endometriotic lesions related to hypoestrogenism and, possibly, to a supplementary anti-angiogenic activity.

Anti-angiogenesis has been considered as an alternative therapeutic approach showing efficacy in endometriosis reduction without side effects on fertility or toxicity profiles. Several anti-angiogenic agents have been tested in experimental endometriosis. In mouse models, rapamycin clearly reduced endometriotic implants, along with diminished VEGF expression and decreased MVD [271]; in the nude mouse model endostatin affected expression of VEGFR2 and/or VEGF isoforms and decreased HIF-1α expression [272], while angiostatin showed a complex mechanism of the inhibition of blood vessel development [273, 274]; anginex demonstrated anti-angiogenic activity in mouse model of endometriosis [274]. In a rat endometriosis model, bevacizumab, VEGF-neutralizing monoclonal antibody, was shown to increase apoptosis [275]. Other drugs with anti-angiogenic effects confirmed in experimental endometriosis are celecoxib, a COX-2 inhibitor [276], and non-toxic fumagillin analogs, semisynthetic derivatives of a natural antibiotic, Aspergillus fumigatus [274]. The results of these

Table 3. Targeted therapy in endometriosis and endometriosis-associated ovarian malignancies

Molecules and pathways	Effect	Therapeutic agent	Targeted action
JAK/STAT [259]	Cell proliferation	Leflunomide Atiprimod	JAK inhibitor STAT3 inhibitor
TGF-β/SMAD [201]	Dual roles in regulation cell proliferation (balance of pro-proliferative and anti-proliferative effects)	Lerdelimumab Metelimumab GC-1008 SD-093 LY-580276	Recombinant human IgG4 targeting TGF-β2 Recombinant human IgG4 targeting TGF-β1 Targets all TGF-β isoforms Small molecule inhibitors of SMAD2/3 activity
MEK/ERK [260]	Regulation of signaling for proliferation, apoptosis, adhesion, invasion, angiogenesis, and evasion of immune surveillance	Selumetinib	Small molecular inhibitor of MEK
VEGF [251, 252, 256]	Growth of tumor vessels	Bevacizumab	Inhibits receptor binding and prevent tumor angiogenesis
		Sunitinib	Multitargeted receptor tyrosine kinase inhibitor (VEGFR, PDGFR, CD117)
PI3K/AKT/mTOR signaling pathway [250]	Lipid kinases that regulate vital signaling pathways in neoplasia	RAD001	mTOR inhibitor
		Temsirolimus	mTOR inhibitor
AnxA4 [255, 261]	Exocytosis and regulation of epithelial Cl^- secretion	AnxA4-neutralizing antibodies	AnxA4 blockade
ARID1A [230–233]	AT-rich interactive domain 1A (SWI-like) gene encodes BAF250A (member of the SWI/SNF ATP-dependent chromatin remodeling complex)	EZH2	EZH2 inhibition upregulates PI3K which negatively regulates PI3K/AKT signals
HNF-1β [102, 208]	Transcription activator expressed also in endometriosis which regulates multiple cancer-related genes	Future inhibitors/inhibitors of genes activated by HNF-1β	HNF-1β inhibitor dipeptidyl peptidase IV inhibitor, osteopontin inhibitor, tissue factor pathway inhibitor 2, AnxA4 inhibitor, and angiotensin-converting enzyme 2 inhibitor
ZNF217 [253, 254]	Gene situated on 20q13.2 encoding a transcription factor in cancers associated with poor prognosis and lymph node metastasis	Triciribine	Inhibitor of ZNF127-overexpressing cells growth

experimental studies represent provide hope for the application of anti-angiogenic therapies in human endometriosis. Promising novel anti-endometriosis drugs are represented by the pro-apoptotic agents, such as apoptosis inducer (arcyriaflavin) [277], apigenin [278], NF-κB inhibitor (PDTC), and proteasome inhibitors (bortezomib) [279] that were tested on human cell lines and rat models.

Final remarks

Due to endometriosis heterogeneity, attributed to genomic and proteomic variability, expressed by variable anatomic location, number, size and duration of implants, carcinogenesis associations, numerous subtypes of endometriosis have been described.

Current trends in genomic and proteomic approaches are useful for a deeper understanding of endometriosis pathogeny and its malignant transformation, a better (re)classification, and a higher potential identification of new therapeutic targets. The putative biomarkers such as P450 aromatase, IL-6, TNF-α, and anti-endometrial cells autoantibodies have been proposed.

Nowadays, the therapy is limited by high frequency of recurrences and the impossibility to preserve

fertility mainly in women who require extensive surgical procedures. Based on molecular analogies between endometriosis and carcinogenesis, numerous studies are ongoing, being currently during variable experimental phases or in clinical trials, as attempts to exploit the therapeutic anti-cancer arsenal in the treatment of endometriosis.

Conflict of interest

The authors declare that they have no conflict of interests.

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