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Pathophysiological mechanisms and next-generation therapeutic opportunities in endometriosis

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Abstract

Endometriosis is a chronic, inflammatory, and heterogeneous disease affecting approximately 10% of women of reproductive age and is a major cause of pelvic pain and infertility. Despite its substantial clinical burden, diagnosis is frequently delayed, and current hormonal and surgical treatments remain non-curative, with recurrence and variable treatment responses being common. These clinical challenges reflect the complex and multifactorial nature of endometriosis, in which hormonal dysregulation, immune dysfunction, hypoxic and metabolic adaptation, and vascular remodeling interact to drive ectopic lesion establishment, persistence, and progression. This review integrates current understanding of the molecular and cellular mechanisms underlying endometriosis pathogenesis. We discuss how enhanced adhesion and invasion facilitate lesion establishment, how dysregulated innate and adaptive immune responses impair the clearance of ectopic endometrial cells and sustain chronic inflammation, and how hypoxia-driven signaling and metabolic reprogramming promote lesion survival. We further examine the roles of aberrant steroid hormone signaling, angiogenesis, and lymphangiogenesis in lesion maintenance and progression, as well as how these interconnected processes contribute to lesion heterogeneity and treatment resistance. Finally, we highlight how emerging multi-omics approaches and patient-derived organoid and assembloid models may facilitate mechanistic validation, biomarker discovery, and therapeutic development. By connecting the mechanisms of lesion initiation and progression with current therapeutic limitations, this review provides a framework for developing more precise, mechanism-based diagnostic and therapeutic strategies.

KEYWORDS
endometriosis, hypoxia, immune dysfunction, inflammation, steroidogenesis

Impact statement

Endometriosis is a chronic disease affecting women of reproductive age, yet no curative medical treatment is currently available. Its chronic symptoms and associated infertility substantially impair quality of life and impose considerable burdens on patients and families, healthcare systems, and society. This review integrates current evidence on the molecular and cellular mechanisms underlying endometriotic lesion establishment, persistence, and progression and highlights how these insights may guide biomarker discovery and the development of more effective, mechanism-based therapies.

Introduction

Endometriosis is defined by the presence of endometrial-like tissue at ectopic sites and encompasses a broad spectrum of anatomical and clinical phenotypes. Approximately 10% of reproductive-aged women are affected, with symptoms ranging from dysmenorrhea, pelvic pain, and dyspareunia to impaired fertility. The disease may manifest as superficial peritoneal lesions, ovarian endometriomas, deep endometriosis, or extrapelvic lesions. These phenotypes may occur independently or concurrently and differ in symptom presentation, anatomical location, diagnostic visibility, and therapeutic requirements. Clinical recognition remains difficult because symptoms vary considerably and overlap with those of gynecological, gastrointestinal, urinary, and other chronic pain conditions. Although advances in transvaginal ultrasonography have improved the identification of ovarian endometriomas and deep lesions, superficial peritoneal disease often escapes detection [1]. Circulating small RNAs and proteins have emerged as promising non-invasive biomarkers for endometriosis, though further clinical validation is required before their implementation in routine practice [2, 3]. Consequently, many patients experience a prolonged interval between symptom onset and definitive diagnosis, extending disease-related morbidity and potentially allowing disease progression in some cases.

Available therapies mainly aim to suppress symptoms and disease activity rather than eliminate the underlying disorder. Combined hormonal contraceptives and progestins are commonly used in patients who are not attempting pregnancy, whereas surgery may be considered for persistent symptoms, suspicious ovarian lesions, or selected reproductive indications. However, hormonal treatment does not remove established lesions and may be limited by contraceptive effects, adverse events, incomplete symptom control, and recurrence after withdrawal [4]. Reduced progesterone responsiveness may further weaken the effectiveness of progestin-based treatment in some patients [5]. Surgical excision can reduce lesion burden but is limited by operative complications, potential loss of ovarian reserve, and the risk of recurrence [4, 6].

The development of endometriosis requires more than the attachment of endometrial cells at ectopic sites. Retrograde menstruation provides a potential route through which endometrial tissue fragments enter the pelvic cavity, but only a subset of these cells can attach, invade, survive, and form persistent lesions [7]. Their establishment and progression are shaped by a supportive lesion microenvironment characterized by hypoxia, altered steroid signaling, chronic inflammation, immune dysfunction, and metabolic adaptation [8–11]. Impaired immune clearance, resistance to apoptosis, and enhanced angiogenesis and

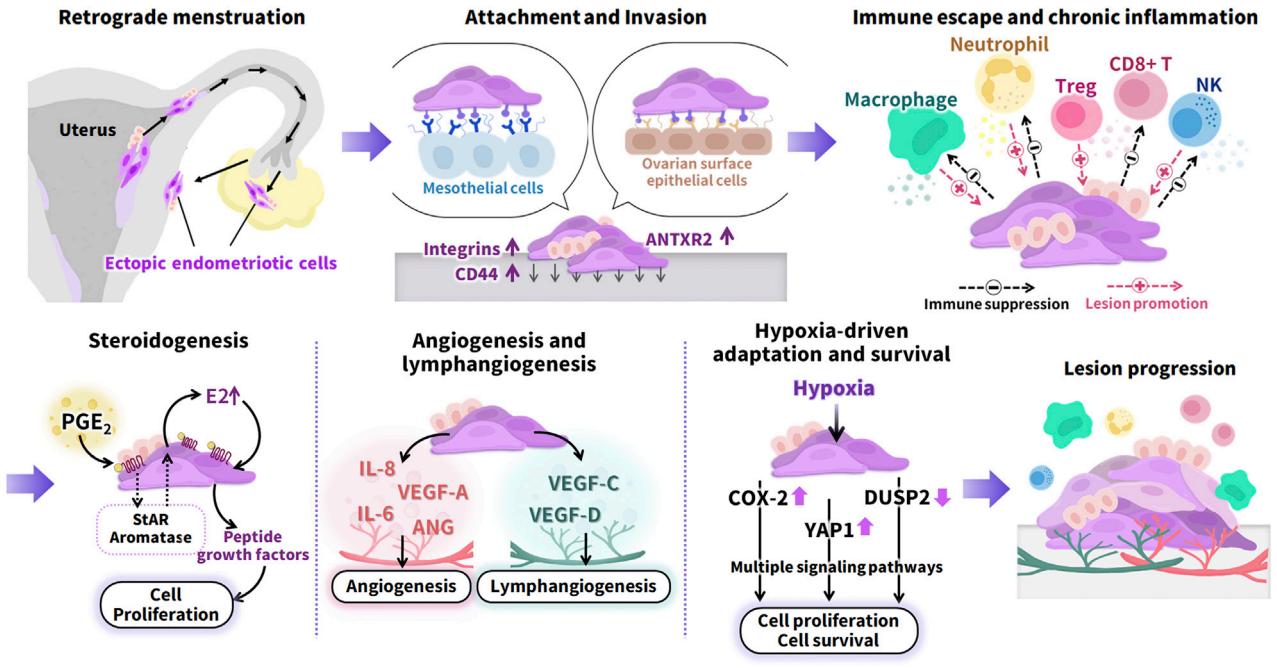


FIGURE 1
Mechanisms underlying endometriotic lesion establishment and progression. Retrograde menstruation transports endometrial cells into the peritoneal cavity. Increased integrin, CD44, and ANTXR2 expression facilitates their attachment to mesothelial or ovarian surface epithelial cells and subsequent invasion. Dysfunctional macrophages, neutrophils, natural killer cells, $CD8^+$ T cells, and regulatory T cells reduce immune clearance and establish a chronic inflammatory, lesion-promoting microenvironment. In established lesions, PGE_2 induces StAR and aromatase, increasing local estradiol synthesis; estradiol and peptide growth factors subsequently stimulate cell proliferation. IL-6, IL-8, VEGF-A, and angiogenin promote angiogenesis, whereas VEGF-C drives lymphangiogenesis. Hypoxia further increases COX-2 and YAP1 activity while suppressing DUSP2, activating multiple signaling pathways that enhance cell proliferation and survival. Together, these interconnected processes support lesion establishment, vascularization, persistence, and progression. Upward and downward arrows indicate increased and decreased expression or activity, respectively; black dashed lines indicate immune suppression, and red dashed lines indicate lesion-promoting effects. Abbreviations: ANG, angiogenin; ANTXR2, anthrax toxin receptor 2; COX-2, cyclooxygenase-2; DUSP2, dual-specificity phosphatase 2; E2, estradiol; NK, natural killer; PGE_2, prostaglandin E_2; StAR, steroidogenic acute regulatory protein; Treg, regulatory T cell; VEGF, vascular endothelial growth factor; YAP1, Yes-associated protein 1.

lymphangiogenesis further promote lesion survival [12–15]. Interactions among these processes shape a microenvironment that supports lesion establishment, persistence, and progression (Figure 1). This interconnected network is further reinforced by reciprocal communication among epithelial, stromal, mesothelial, immune, and endothelial cells within the lesion microenvironment. Nevertheless, it remains unclear why distinct lesion phenotypes develop, why disease burden correlates poorly with symptom severity, and why treatment responses vary substantially among patients.

This review comprehensively summarizes the cellular and molecular mechanisms governing lesion establishment, persistence, and progression, with emphasis on how interactions among immune dysfunction, hypoxia, steroid signaling, metabolic adaptation, and vascular remodeling shape the lesion microenvironment. By organizing these mechanisms according to the key biological processes of lesion development, we further discuss how current mechanistic insights may guide the development of more effective, mechanism-based therapeutic strategies.

Initiation and establishment of ectopic lesions

Cellular origins and etiology

The cellular origins and establishment of endometriosis are complex, and several hypotheses have been proposed to explain how ectopic lesions arise. Among them, Sampson's retrograde menstruation hypothesis remains the most widely accepted [7]. It proposes that viable menstrual tissue refluxes through the fallopian tubes into the peritoneal cavity, where endometrial fragments attach to the mesothelial surface and proliferate at ectopic sites such as the ovaries, peritoneum, and bowel (Figure 1) [7]. Sampson's theory provides a central framework for understanding endometriosis but does not fully explain the mechanisms underlying lesion development. For example, retrograde menstruation occurs in most women, whereas only a subset develops endometriosis, indicating that refluxed tissue alone is insufficient to cause endometriosis. Lesion establishment also requires intrinsic biochemical alteration of the shed endometrial cells and a permissive peritoneal microenvironment to enhance adhesion and invasion [11, 16].

Development from Müllerian remnants and coelomic metaplasia represent two additional plausible origins of endometriosis. The Müllerian remnant hypothesis proposes that primitive Müllerian cells are misplaced or persist at ectopic sites during embryonic development [17]. These dormant cells may later respond to estrogen and differentiate into endometrial-like glands and stroma. In contrast, coelomic metaplasia proposes that peritoneal mesothelial cells or ovarian surface epithelial cells [18], which share an embryological origin with Müllerian tissues, acquire an endometrial-like phenotype under hormonal, inflammatory, or other local stimuli. These hypotheses may help explain lesions that are difficult to attribute solely to retrograde menstruation, including some deep or extrapelvic lesions. Morphological transitions between mesothelium and ectopic tissue, together with the formation of endometrial-like glandular structures from ovarian surface epithelial cells *in vitro*, provide experimental support for metaplasia. However, clinical evidence supporting these alternative origins remains limited, and their relative contribution to endometriosis pathogenesis remains uncertain.

In summary, the etiology and cellular origins remain inconclusive even though the term "endometriosis" has been defined for more than 100 years [19]. Based on clinical features and biochemical characteristics, the aforementioned hypotheses may account for one or some disease etiology, but none can satisfactorily explain the heterogeneity of different types of lesions. In the following sections, we will employ the widely accepted retrograde menstruation theory as the model to discuss the biological processes and underlying mechanisms of ectopic lesion formation and maintenance.

Attachment, invasion, and interaction with peritoneal tissues

Adhesion to tissues of peritoneal organs is a critical early step in ectopic lesion formation. Retrograded endometrial cells interact with mesothelial and ovarian tissues, as well as with extracellular matrix components, through mechanisms including hyaluronan-CD44 and laminin-integrin α6β1 binding (Figure 1) [20, 21]. The adhesion process is further enhanced by transforming growth factor beta 1 (TGF-β1) through a sialic acid–dependent glycan–receptor interaction [22]. Extracellular matrix components, including collagen IV, fibronectin, laminin, and hyaluronan are also critical molecules for the adhesion of endometrial cells to peritoneal organs. Epithelial-stromal interactions and increased matrix stiffness further enhance this adhesion, potentially facilitating the early establishment of ovarian endometrioma [23]. Anthrax toxin receptor 2 (ANTXR2), a receptor for collagen IV and laminin, was found to be upregulated in ectopic endometriotic stromal cells and plays a critical role in facilitating cell adhesion. Hypoxia induced chromatin remodeling at the *ANTXR2* locus leading to aberrant expression of ANTXR2. By interacting with extracellular matrix molecules such as collagen IV and laminin, activation of ANTXR2 signaling increased Yes-associated protein 1 (YAP1) nuclear translocation and transcriptional upregulation of numerous genes contributing to the pathological processes of endometriosis. Genetic or pharmacological inhibition of ANTXR2 reduced cell adhesion, prevented lesion formation, and decreased the burden of established lesions in mouse models [24], supporting a functional role of ANTXR2 in endometriotic lesion formation.

Following attachment, endometrial cells invade into the underlying tissue. Endometrial stromal cells derived from both eutopic and ectopic tissues of women with endometriosis exhibit enhanced motility and transmesothelial invasion. Although less invasive on their own, epithelial cells further promote stromal-cell invasion in a coculture system [25]. Connexin-43-mediated gap-junction communication between endometrial stromal cells and peritoneal mesothelial cells may transmit signals that weaken mesothelial barrier integrity and facilitate tissue penetration [25]. Ectopic epithelial cells may also acquire epithelial-to-mesenchymal transition (EMT)-like features that further support invasion [26]. Peritoneal mesothelial cells further enhanced the motility of

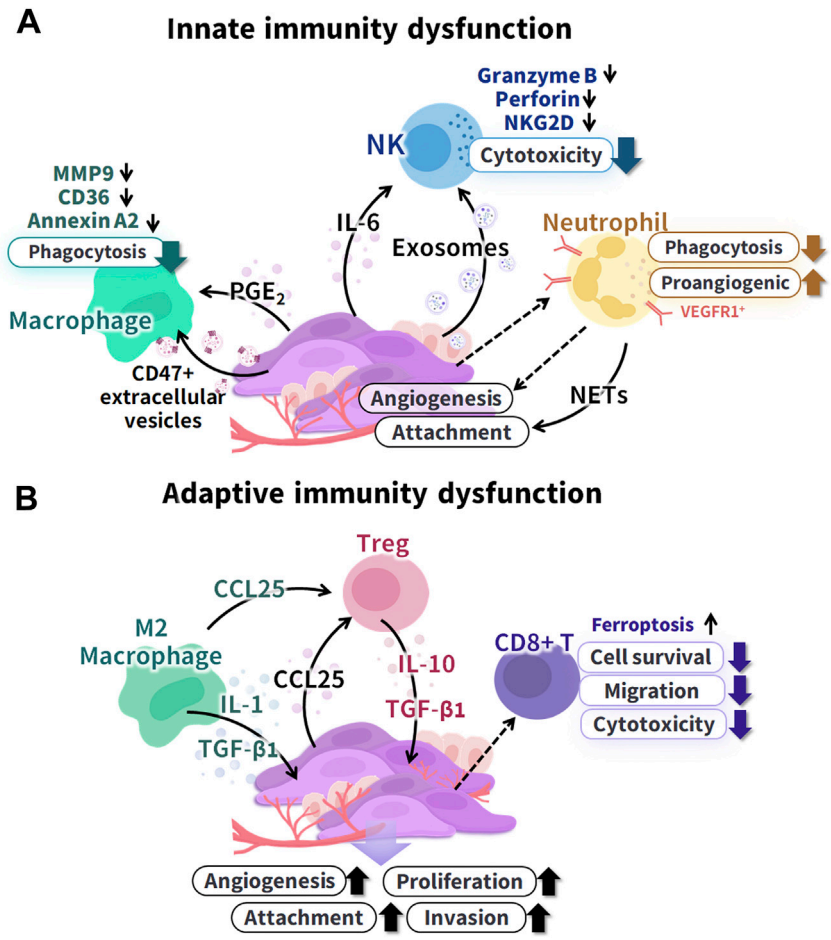


FIGURE 2
Innate and adaptive immune dysfunction promotes endometriotic lesion development. **(A)** PGE_2 and $CD47^+$ small extracellular vesicles impair macrophage phagocytosis by reducing MMP9, CD36, and annexin A2. IL-6 and lesion-derived exosomes suppress NK-cell cytotoxicity by reducing granzyme B, perforin, and NKG2D. Neutrophils exhibit reduced phagocytosis, whereas increased $VEGFR1^+$ proangiogenic neutrophils and NETs may promote angiogenesis and tissue attachment. **(B)** M2-like macrophages promote Treg differentiation through CCL25 and support lesions through IL-1 and TGF-β1. CCL25 is also secreted by ectopic stromal cells. Treg-derived IL-10 and TGF-β1 further promote lesion progression. Increased ferroptosis reduces $CD8^+$ T-cell survival, migration, and cytotoxicity. These immune alterations collectively enhance lesion attachment, angiogenesis, proliferation, and invasion. Solid arrows indicate established effects, dashed arrows indicate indirect or incompletely defined relationships. Upward and downward arrows indicate increases and decreases, respectively. Abbreviations: CCL25, C-C motif chemokine ligand 25; MMP9, matrix metalloproteinase 9; NETs, neutrophil extracellular traps; NK, natural killer; NKG2D, natural killer group 2 member D; PGE_2, prostaglandin E_2; TGF-β1, transforming growth factor-β1; Treg, regulatory T cell; VEGFR1, vascular endothelial growth factor receptor 1.

endometriosis-derived endometrial stromal cells and induced connexin 43-mediated gap-junction communication with them. Blocking this intercellular communication reduced transmesothelial invasion, suggesting that direct endometrial-mesothelial signaling facilitates tissue penetration [27]. Recent single-cell RNA sequencing (scRNA-seq) analysis reveals that in deep endometriosis, mesothelial cells show higher expression of EMT-associated genes compared to the mesothelial cells from peritoneal endometriosis and ovarian endometriosis. EMT in mesothelial cells might disrupt the integrity of the mesothelium, potentially facilitating the infiltration of endometrial cells into deeper tissue layers [28]. These findings support a model in which reciprocal interactions among endometrial cells, mesothelial cells, and the extracellular matrix promote adhesion and tissue invasion, thereby facilitating lesion establishment and deep infiltration.

Immune escape and chronic inflammation

Mechanisms of innate immunity dysfunction

Innate immunity is the first-line defense system that destroys foreign entities and body's own injured, infected, cancerous, or dying cells. Macrophages, neutrophils, and natural killer (NK) cells are key components of innate immune surveillance that contribute to the clearance of refluxed endometrial cells and tissues. However,

disease-associated functional changes of these immune cells impair the clearance of refluxed endometrial cells and create a microenvironment favorable for lesion survival (Figure 2A). Under physiological conditions, macrophages maintain peritoneal homeostasis by recognizing, engulfing, and degrading shed endometrial fragments. This process is mediated by coordination of matrix metalloproteinase (MMP), scavenger receptors such as CD36, and annexin A2. Macrophages secrete MMPs to digest the extracellular matrix of retrograded tissues and dissociate them into small fragments, whereas upregulation of scavenger receptors promotes phagocytosis. In endometriosis, macrophages isolated from peritoneal fluid display a marked reduction in phagocytic capability compared to those isolated from endometriosis-free women [29]. A series of studies reveal that aberrant production of cyclooxygenase-2 (COX-2)-dependent prostaglandin E_2 (PGE_2) by ectopic endometriotic stromal cells [30] and macrophages [31] suppresses the expression and functions of MMP-9, CD36, and annexin A2 in macrophages. As a result, the phagocytic ability of macrophages was markedly inhibited, which may facilitate the persistence of refluxed endometrial fragments in the peritoneal cavity [14, 29, 32, 33]. A recent study further showed that small extracellular vesicles released by ectopic endometrial epithelial cells carry CD47, which engages signal-regulatory protein-α on macrophages and delivers an inhibitory "do not eat me" signal [34]. Blocking CD47 restored macrophage phagocytosis, supporting the functional importance of this immune-evasion mechanism.

NK-cell immune surveillance is similarly impaired in endometriosis. NK cells exhibit reduced cytotoxicity and chemotaxis, together with enrichment of the less cytotoxic $CD56^{bright}CD16^{dim}$ subset, increased inhibitory-receptor expression, and reduced activating-receptor expression [35–37]. Elevated IL-6 in the peritoneal fluid reduces granzyme B and perforin production, thereby impairing NK cell-mediated clearance of ectopic cells [38]. Recurrent bleeding and tissue injury also activate platelets within ectopic lesions. Platelet-derived TGF-β1 downregulates the NK-cell activating receptor natural killer group 2 member D (NKG2D), protecting ectopic cells from NK-cell-mediated cytotoxicity [39]. Ectopic tissue-derived exosomes further suppress cytotoxic surveillance by carrying NKG2D ligands that act as decoys, resulting in NKG2D downregulation and impaired cytotoxicity [40]. These mechanisms allow ectopic endometrial cells to evade NK-cell-mediated elimination.

Neutrophils are the most abundant circulating leukocyte population and are the first recruited immune cells during the development of endometriosis in human and mouse models of endometriosis [41, 42]. However, peripheral blood neutrophils from endometriosis patients demonstrate significantly reduced phagocytic function [43]. Importantly, this immune defect is reversible; surgical excision of ectopic lesions restores peripheral neutrophil phagocytic function to levels comparable to healthy controls within 1 week post-operatively [43]. This phagocytic dysfunction is directly mediated by circulating factors, as exposing healthy control neutrophils to plasma from endometriosis patients decreases their phagocytic capacity [44]. In contrast, the phagocytic ability of peripheral blood neutrophils from endometriosis patients can be improved when exposed to plasma from individuals without endometriosis [44]. This reduced phagocytic capacity may facilitate the survival of retrograde endometrial cells within the pelvic compartment.

Besides the reduced phagocytic ability of neutrophils in patients with endometriosis, the ratios of aged (expressing CXCR2) and proangiogenic (expressing CXCR2 and VEGFR1) neutrophils are significantly increased within patient menstrual effluent [45]. In murine models, blocking neutrophil recruitment with α-CXCR2 antibodies during the early stages of disease dramatically impairs tissue adhesion and reduces both the number and total weight of developing lesions [45]. This early attachment is facilitated by neutrophil extracellular traps (NETs) and their byproducts, myeloperoxidase and neutrophil elastase. These secretions interact with upregulated endometrial fibrinogen, forming a provisional adhesive matrix or "molecular glue" that enables cell adhesion to the mesothelium [45]. Early lesion establishment is further supported by an immune-predominant initiation phase (<72 h) characterized by a surge in peritoneal cytokines, including G-CSF, IL-6, and the proangiogenic factor, vascular endothelial growth factor (VEGF) [42].

Mechanisms of adaptive immunity dysfunction

Ectopic lesions also alter the abundance and functional states of macrophage subpopulations [46]. A scRNA-seq analysis identified an enrichment of *LYVE1*-positive macrophages in eutopic and ectopic tissues from women with endometriosis. These tissue-resident, perivascular macrophages express tolerogenic, pro-angiogenic, and neurotrophic transcriptional programs, consistent with potential roles in immune tolerance, vascularization, and pain development [46]. Lesion-derived extracellular vesicles provide another mechanism of macrophage reprogramming. Exosomes released from stromal cells derived from mice with endometriosis induced an M2-like phenotype with reduced phagocytic activity, and their intraperitoneal administration increased lesion weight in a mouse model [47]. Integrative scRNA-seq and genetic analyses further implicated M2-like macrophages as mediators of germline endometriosis risk and identified them as an important hub of IL-1-associated communication between immune and lesion cells [48]. In endometrial epithelial organoid-stromal co-cultures, IL-1β disrupted epithelial differentiation, whereas IL-1 receptor blockade reduced pain, fibrosis, angiogenic-factor expression, and lesion burden in mice [48]. Macrophage-mediated stromal reprogramming has also been linked to bacterial infection. *Fusobacterium* infection increased the infiltration of TGF-β1-producing M2-like macrophages and promoted the transition of endometrial fibroblasts into *TAGLN*-positive myofibroblasts. These cells exhibited enhanced proliferative, adhesive, and migratory properties (Figure 2B) [49, 50]. TGF-β1 is a key mediator of myofibroblast transdifferentiation, and activated myofibroblasts subsequently produce excessive extracellular matrix components that promote fibrosis [51]. Fibrosis is an important pathological feature of endometriotic lesions. Mesothelial cells, endometrial fibroblasts, and endometrial epithelial cells have been proposed as potential precursor cells of myofibroblasts [52–54]. Macrophages are reported to contribute to lesion fibrogenesis. In a mouse model of endometriosis, macrophage depletion reduced lesional macrophage infiltration and fibrotic content. Conversely, adoptive transfer of M2a macrophages, a subtype of M2 macrophages, but not M1 or M2c macrophages, markedly increased lesion fibrosis, supporting a specific profibrotic role of M2a macrophages [55]. Persistent TGF-β1 signaling and myofibroblast activation may therefore link chronic inflammation

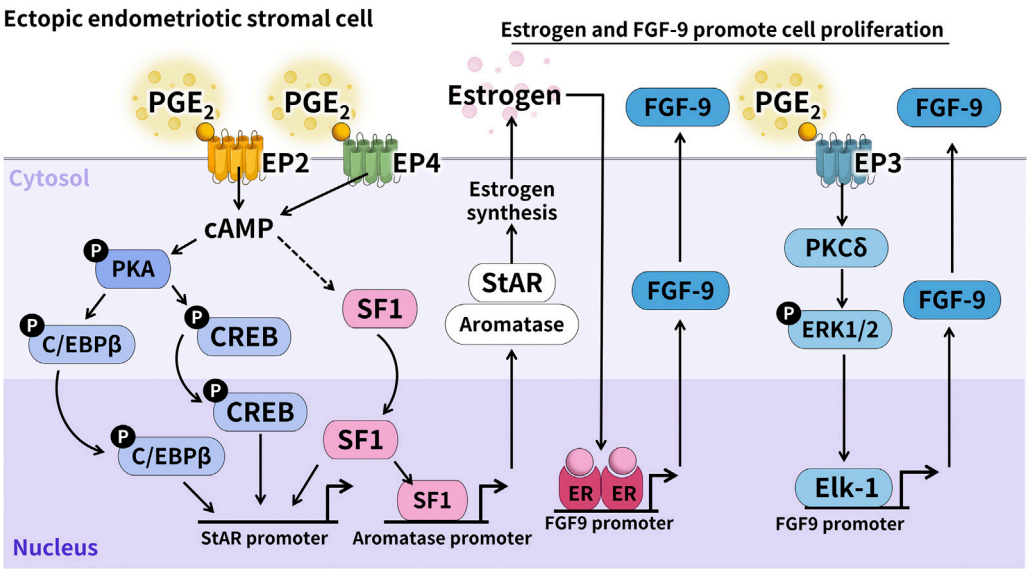


FIGURE 3
PGE_2-driven steroidogenesis and FGF-9 signaling in ectopic endometriotic stromal cells. PGE_2 activates EP2/EP4–cAMP–PKA signaling to induce C/EBPβ- and CREB-dependent StAR expression and promotes SF1-dependent aromatase expression, thereby increasing estrogen synthesis. Estrogen–ER signaling subsequently induces FGF-9 expression. In parallel, PGE_2 activates EP3–PKCδ–ERK1/2–Elk-1 signaling to increase FGF-9 expression. These pathways collectively promote stromal-cell proliferation. Solid arrows indicate established effects, dashed arrows indicate indirect or incompletely defined relationships. Abbreviations: C/EBPβ, CCAAT/enhancer-binding protein β; cAMP, cyclic adenosine monophosphate; CREB, cAMP response element-binding protein; Elk-1, ETS transcription factor Elk-1; EP2/EP3/EP4, prostaglandin E_2 receptors 2, 3, and 4; ER, estrogen receptor; ERK1/2, extracellular signal-regulated kinases 1 and 2; FGF-9, fibroblast growth factor 9; PGE_2, prostaglandin E_2; PKA, protein kinase A; PKCδ, protein kinase Cδ; SF1, steroidogenic factor 1; StAR, steroidogenic acute regulatory protein.

to progressive fibrogenesis in endometriotic lesions. Progressive fibrosis can contribute to tissue and organ dysfunction, and the extent of lesional fibrosis has been positively correlated with the severity of dysmenorrhea [56].

Endometriosis is also associated with altered T-cell composition and function (Figure 2B). A reduced proportion of effector CD8-positive T cells and diminished activation may weaken immune surveillance and support lesion persistence [37, 57, 58]. Ectopic stromal cells induce CD8-positive T-cell dysfunction through activation of the programmed cell death protein 1-dependent pathway and glycolytic metabolic reprogramming, reducing T-cell proliferation and cytotoxicity [58]. In addition, iron released by recurrent ectopic bleeding induces ferroptosis in CD8-positive T cells, impairing their migration and cytotoxic function and thereby promoting disease progression [59]. Conversely, regulatory T cells (Tregs) are increased in the peritoneal fluid of women with endometriosis, particularly in advanced disease. CCL25 produced by ectopic stromal cells and macrophages, promotes Treg differentiation and immunosuppressive activity [60], whereas estrogen-induced indoleamine 2,3-dioxygenase 1 further favors Treg differentiation within the ectopic microenvironment [61]. Through IL-10-, TGF-β-, and CD73-dependent signaling, these Tregs promote endometrial stromal-cell proliferation and invasion, accompanied by increased MMP2 and reduced TIMP1 expression [60]. Endometriosis therefore combines chronic inflammation with defective immune surveillance. Impaired macrophage phagocytosis, weakened NK- and CD8-positive T-cell cytotoxicity, and enhanced Treg activity allow ectopic cells to evade clearance while supporting lesion development.

Mechanisms driving lesion survival and progression

Steroidogenesis

Female sex hormones (estrogen and progesterone) are indispensable for the proliferation and differentiation of endometrial cells, which also applies to ectopic endometriotic cells [62]. However, during the period of menstruation when the level of sex hormones is at the nadir, endometrial tissues regress while ectopic endometriotic lesions survive. This phenomenon indicates that ectopic endometriotic lesions may develop a self-maintaining system to support their survival. Indeed, researchers found that ectopic endometriotic stromal cells are capable of producing progesterone and estrogen by expressing necessary steroidogenic proteins and enzymes [63, 64]. Two key proteins controlling steroidogenesis, steroidogenic acute regulatory protein (StAR) and aromatase, are upregulated by prostaglandin E_2 (PGE_2) in ectopic endometriotic stromal cells [65, 66]. StAR mediates cholesterol transport into mitochondria, the first rate-limiting step in steroid hormone synthesis, while aromatase catalyzes the last step of steroidogenesis by converting testosterone to estradiol.

Through the EP2 receptor, PGE_2 activates cAMP-protein kinase A (PKA)-CREB signaling and promotes StAR transcription [67], and this effect is facilitated via acetylation of histone H3 bound to the StAR promoter [68]. Besides CREB, PGE_2 also stimulates StAR expression via the other two transcription factors, C/EBP-β and steroidogenic factor-1 [63, 67] (Figure 3). On the other hand, PGE_2 induces aromatase expression by selectively enhancing the binding of steroidogenic factor-1 to the alternative promoter II of aromatase gene [69]. More importantly, PGE_2-induced StAR and aromatase expression only occurs in ectopic endometriotic stromal cells but not the normal endometrial stromal cells [65, 66]. As a result, PGE_2-driven upregulation of StAR protein and aromatase in ectopic endometriotic stromal cells creates an estrogen-rich local environment that supports lesion survival and growth.

Estrogen is required for ectopic lesion survival and growth but is not a mitogen *per se*. Estrogen-induced endometriotic cell proliferation may therefore be mediated by downstream effectors, particularly peptide growth factors. Several peptide growth factors, such as insulin-like growth factor-1, epidermal growth factor, and fibroblast growth factors (FGFs), were found to exert mitogenic effects on endometrial cells [70–72]. Among these, FGF-9 was found to be regulated by estrogen and is responsible for estrogen-induced endometrial stromal cell proliferation [73]. The expression levels of FGF-9 and its cognate receptors, FGFR2-IIIc and FGFR3-IIIc, were correlated with the estradiol concentrations in the peritoneal fluid of women with endometriosis [73]. Administration of anti-FGF-9 antibodies abolished estrogen-induced stromal-cell proliferation, whereas FGF-9 supplementation rescued the proliferation inhibited by an estrogen receptor antagonist [72, 73]. FGF-9 binds to FGFR2 to activate ERK signaling and mammalian target of rapamycin/S6K1 signaling to induce stromal cell proliferation [74]. Interestingly, PGE_2 can directly stimulate FGF-9 expression via EP3-mediated protein kinase Cδ, which provides an alternative way to ensure the sustained growth of endometriotic cells [75].

Angiogenesis and lymphangiogenesis

As shed-off endometrial tissues retrograde to the peritoneal cavity, hypoxia is an inevitable stress these cells encounter. To overcome this detrimental stress, endometrial cells must establish a new vascular supply once attached to the surface of pelvic organs. Angiogenesis, the formation of new blood vessels from pre-existing vasculature, is governed by the balance between pro- and anti-angiogenic signals. Pro-angiogenic mediators, including VEGF, FGF, angiopoietins, angiogenin, leptin, and inflammatory cytokines, activate endothelial cells through multiple receptor pathways to promote proliferation, migration, survival, and vascular remodeling [76, 77]. Women with endometriosis exhibit elevated levels of VEGF-A, FGF-9, IL-8, IL-6, leptin, and angiogenin in ectopic lesions and/or peritoneal fluid [78–82]. These angiogenic factors help reconstruct the vascular network to supply the oxygen and nutrients required for lesion survival and growth.

The expression and function of VEGF-A have been well documented in the literature. Estrogen, proinflammatory cytokines, and the hypoxic microenvironment were reported to regulate VEGF-A expression in endometriotic cells [83–85]. Inhibition of VEGF signaling with antibodies or VEGF-receptor antagonists has shown lesion-regressive effects in preclinical models, whereas human evidence remains very limited [86]. Leptin is not a canonical angiogenic factor, but ablating leptin signaling leads to endometriotic lesion regression in a murine model of endometriosis, possibly due to inhibiting cell proliferation and neoangiogenesis [87]. Elevated leptin in endometriotic stromal cells induces both cell proliferation and leptin gene expression [88]. This positive feedback may contribute to sustained leptin overexpression in endometriotic stromal cells. IL-6 and IL-8, on the other hand, are emerging as potent angiogenic factors besides their well-known proinflammatory functions. In endometriotic stromal cells, both IL-6 and IL-8 were found to be upregulated by similar mechanisms and play an important role in angiogenesis [79, 80]. Hypoxia suppresses the expression of dual specificity phosphatase-2 (DUSP2), leading to prolonged activation of ERK signaling, which ultimately results in transcriptional upregulation of IL-6 and IL-8. Elevating IL-6 and IL-8 concentrations in ectopic lesions and peritoneal fluid were linked to increased endometriotic cell proliferation and angiogenesis. Hypoxia also reduces the expression of chicken ovalbumin upstream promoter-transcription Factor II (COUP-TFII), a transcriptional repressor of angiogenin. Loss of COUP-TFII increases angiogenin production and secretion by ectopic stromal cells, promoting endothelial-cell invasion and tube formation [13]. In parallel, the iron-rich and oxidative lesion microenvironment provides an additional angiogenic stimulus. Iron overload-induced ferroptosis activates MAPK signaling and promotes the paracrine secretion of VEGF-A and IL-8 from ectopic stromal cells, which subsequently stimulate endothelial tube formation [89].

Immune cells within the ectopic microenvironment contribute not only to inflammation but also to vascular remodeling. ScRNA-seq analysis of tissues from women with endometriosis revealed increased endothelial and mural cell populations in peritoneal lesions. *LYVE1*-positive macrophages localized near blood vessels and expressed pro-angiogenic factors, suggesting that stromal and immune cells may contribute to lesion vascularization [46]. During early lesion establishment, inflammatory chemokines recruit and activate neutrophils and macrophages, whereas TNF-α and IL-6 enhance their production of VEGF, creating a positive feedback loop that reinforces angiogenesis [41]. In a murine model of endometriosis, dendritic cells accumulated near newly formed vessels and promoted endothelial cell migration and lesion growth, suggesting that dendritic cells also support disease progression through pro-angiogenic activity [90].

Lymphangiogenesis, the formation of new lymphatic vessels from pre-existing lymphatics, is driven primarily by VEGF-C and VEGF-D signaling through receptors on lymphatic endothelial cells. Peritoneal endometriotic lesions exhibit a modest but significant increase in lymphatic vessel density, accompanied by VEGF-C and VEGF-D expression, supporting the presence of active local lymphangiogenesis [91]. Newly formed lymphatic vessels may facilitate the trafficking of macrophages, dendritic and other myeloid cells, NK cells, cytotoxic T cells, and Treg cells into and around ectopic lesions. These infiltrating immune cells can, in turn, release inflammatory and angiogenic mediators, establishing a reinforcing cycle that sustains inflammation, vascular remodeling, and lesion progression. Deep infiltrating lesions similarly exhibit markedly increased lymphatic vessel density and strong VEGF-C

and VEGF-D expression. This expanded lymphatic network may provide a route for endometriosis-like cells to enter regional lymphatic vessels and lymph nodes, potentially contributing to their locoregional dissemination and persistence [92]. Inflammatory cytokines such as IL-1β, TGF-β, and TNF-α induce *VEGFC* expression via COUP-TFII downregulation [15]. VEGF-C is subsequently released in exosomes and microvesicles, which stimulates lymphatic endothelial cell migration and tube formation. Consistent with the functional importance of this pathway, treatment with Lenvatinib, a VEGFR2/3 inhibitor, reduced immune-cell infiltration and lesion growth in a mouse model of endometriosis [15]. Ectopic stromal cells also secrete exosomes containing the long noncoding RNA HIF1A-AS2, which increases VEGF-D expression in endothelial cells and may further enhance lymphangiogenic signaling within lesions [93]. Taken together, dysregulated VEGF-C/VEGF-D signaling establishes a lymphangiogenic network that connects stromal-cell signaling, vascular remodeling, immune-cell trafficking, and the persistence of endometriotic lesions.

Metabolic adaptation

Under hypoxic and nutrient-limited conditions, ectopic stromal cells undergo metabolic reprogramming to adapt to the hostile lesion microenvironment. Rather than relying exclusively on a single energy source, these cells increase glycolytic activity while retaining oxidative pathways, including fatty acid β-oxidation. ScRNA-seq analyses have further identified altered HIF-1 and AMPK signaling in ectopic stromal cells, together with increased expression of genes involved in both glycolytic and oxidative metabolism [94]. This metabolic flexibility may allow stromal cells to maintain energy production under fluctuating oxygen and nutrient availability, thereby supporting their proliferation, survival, and persistence.

Glycolytic reprogramming is particularly important during the early establishment of ectopic lesions, when refluxed endometrial cells are separated from their original blood supply. HIF-1α increases glucose uptake by inducing glucose transporter expression [95] and upregulates PDK1 [10], which limits mitochondrial pyruvate oxidation and redirects pyruvate toward lactate production. This metabolic shift protects ectopic stromal cells from apoptosis induced by oxidative stress and nutrient deprivation [10]. In addition, PIM2 kinase stabilizes 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 4, further enhancing glycolysis and promoting stromal-cell proliferation, migration, and lesion growth [96]. These findings indicate that metabolic plasticity enables ectopic stromal cells to withstand metabolic stress and sustain lesion progression.

Hypoxia-driven adaptation and survival

As discussed above, elevation of PGE_2 in women with endometriosis plays multifaceted roles in immune escape, angiogenesis, and ectopic lesion development and growth. Biosynthesis of PGE_2 is controlled by the rate-limiting enzyme COX, which converts arachidonic acid to PGH_2, the common precursor of 2-series prostanoids such as PGE_2, $PGF_{2\alpha}$, PGI_2, and thromboxane A2. There are two isoforms of COX: the constitutively expressed COX-1 and the inducible COX-2. Overexpression of COX-1 and COX-2 has been identified in peritoneal macrophages isolated from women with endometriosis, which is associated with the severity of the disease [31]. High concentrations of TNF-α, IL-1β, or even PGE2 itself induce COX-2 elevation in endometriotic peritoneal macrophages, creating a vicious cycle. More importantly, COX-2 was found to be upregulated in ectopic endometriotic stromal cells. It is shown that the COX-2 promoter in endometriotic stromal cells is at least 100 times more sensitive to IL-1β challenge as compared to its normal counterpart [30]. This is likely mediated by the epigenetic and biochemical changes caused by hypoxic stress during the transition of normal endometrial stromal cells to ectopic endometriotic stromal cells [97].

Hypoxia is a detrimental stress as oxygen is required for oxidative phosphorylation to provide energy for maintaining critical biological processes. Under low-oxygen conditions, cells activate adaptive programs to safeguard their survival to avoid apoptosis. In endometriotic cells, upregulation of COX-2, an immediate early gene, to generate large amounts of PGE2 seems to be an efficient way to prevent cell death and increase nutrient and oxygen supply [9]. Endometriotic stromal cells employ several distinct mechanisms to ensure the upregulation of COX-2 (Figure 4). Besides proinflammatory cytokines [30], hypoxia suppresses DUSP2 to cause activation of ERK and p38 MAPK to induce COX-2 overexpression [98]. Hypoxia suppresses DUSP2 through two distinct mechanisms. HIF-1α directly represses DUSP2 transcription by binding to its promoter [98], whereas hypoxia-induced miR-20a promotes DUSP2 mRNA degradation [80]. Both cause DUSP2 downregulation and thus the prolonged activation of ERK and p38 MAPK, resulting in COX-2 overexpression. A second mechanism involves hypoxia-mediated suppression of the transcriptional repressor COUP-TFII. In normal endometrial stromal cells, COUP-TFII binds to the COX-2 promoter and suppresses its transcription. Under hypoxic conditions or in ectopic endometriotic cells, reduced COUP-TFII expression relieves this repression, thereby increasing COX-2 transcription and protein expression [99]. A third mechanism involves YAP1, a transcriptional co-regulator of multiple physiological processes. Hypoxia promotes YAP1 activation through HIF-1α-dependent suppression of large tumor suppressor kinase 1. Activated YAP1 translocates to the nucleus where it cooperates with transcription factors such as TEAD-family proteins to induce COX-2 expression [100].

The activation of YAP1 by hypoxia in endometriotic stromal cells was further discovered to contribute to cell proliferation, survival, migration, inflammation, angiogenesis, and lymphangiogenesis by regulating genes such as *FGF9, DUSP2, PTGS2, IL1B,* and *VEGFC* [100]. Hypoxia-induced YAP1 leads to miR-21-5p upregulation, which contributes to progesterone resistance by suppressing progesterone receptor (PR) expression [101] and promotes autophagy and cell survival by downregulating cell division cycle 25A [102]. These findings establish the HIF-1α-YAP1 axis as an important mechanism linking hypoxic adaptation to lesion survival and progression (Figure 4).

Hypoxia also promotes disease progression through additional pathways. HIF-1α shifts estrogen signaling toward an estrogen receptor (ER) β-dominant state by increasing ERβ and reducing ERα, potentially promoting lesion survival and progesterone

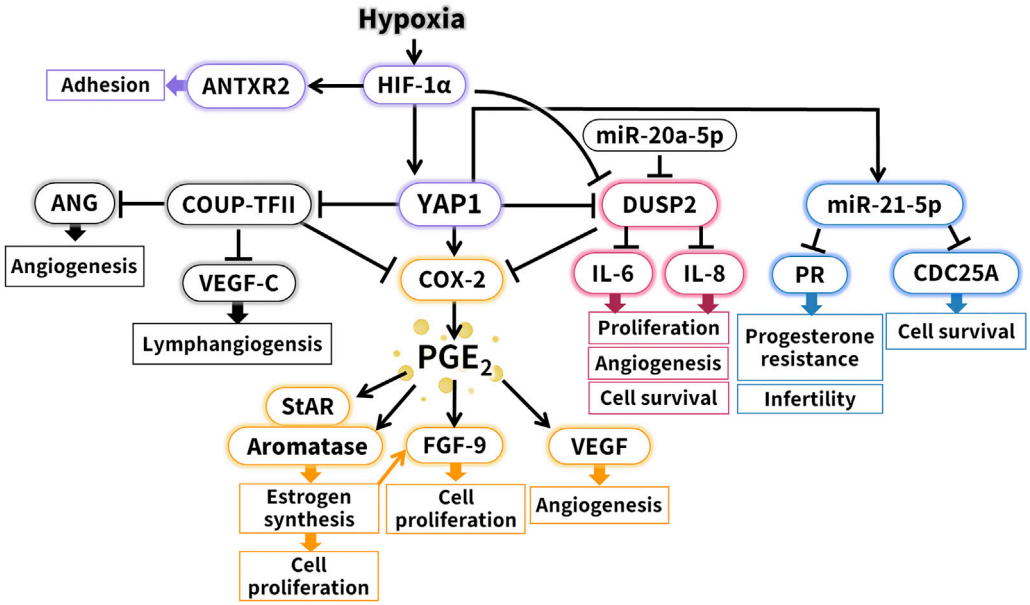


FIGURE 4
Hypoxia-driven adaptation promotes endometriotic lesion survival and progression. Hypoxia activates HIF-1α, inducing ANTXR2-dependent adhesion and YAP1 signaling. YAP1 increases COX-2–PGE_2 signaling, while HIF-1α, YAP1, and miR-20a-5p suppress DUSP2, further increasing COX-2, IL-6, and IL-8. Loss of COUP-TFII enhances angiogenin, VEGF-C, and COX-2 expression. PGE_2 promotes StAR- and aromatase-dependent estradiol synthesis, FGF9-mediated proliferation, and VEGF-dependent angiogenesis. YAP1-induced miR-21-5p suppresses PR and CDC25A, contributing to progesterone resistance, infertility, and cell survival. These interconnected pathways promote lesion adhesion, proliferation, vascularization, and persistence. Abbreviations: ANG, angiogenin; ANTXR2, anthrax toxin receptor 2; CDC25A, cell division cycle 25A; COUP-TFII, chicken ovalbumin upstream promoter-transcription factor II; COX-2, cyclooxygenase-2; DUSP2, dual-specificity phosphatase 2; FGF9, fibroblast growth factor 9; HIF-1α, hypoxia-inducible factor 1α; IL, interleukin; miR, microRNA; PGE_2, prostaglandin E_2; PR, progesterone receptor; StAR, steroidogenic acute regulatory protein; VEGF, vascular endothelial growth factor; YAP1, Yes-associated protein 1.

resistance [103]. Hypoxia-induced loss of DNA methyltransferase 1 causes global DNA hypomethylation, and thus the aberrant expression of pro-survival genes such as *GATA6*, *HOXA3*, and *SLC16A5* [104]. These findings support an important role for hypoxia in the molecular adaptations associated with ectopic lesion survival and progression.

Translational implications and therapeutic opportunities

Unmet needs of endometriosis therapy

Current treatments for endometriosis primarily aim at suppressing disease-associated symptoms rather than eradicating the disease. Combined hormonal contraceptives (estradiol and progesterone) and progestins are commonly used as first-line therapies, whereas gonadotropin-releasing hormone agonists or antagonists are generally considered when initial treatment is ineffective [105]. Although these approaches can reduce pain, treatment responses vary substantially, and symptoms frequently recur after discontinuation. Approximately one-quarter to one-third of patients experience an inadequate response to first-line hormonal therapy [5]. Moreover, hormonal treatments suppress ovulation and are therefore unsuitable for patients actively attempting pregnancy, while long-term use may be limited by irregular bleeding, mood changes, vasomotor symptoms, and reduced bone mineral density [106]. Surgical excision can reduce lesion burden and pain but does not eliminate the risk of recurrence and may cause operative complications, pelvic adhesions, or damage to healthy tissue [105, 107]. Surgery for ovarian endometriomas is particularly concerning because cystectomy may compromise ovarian reserve, with reductions in serum anti-Müllerian hormone of approximately 40% after unilateral surgery and 57% after bilateral surgery [6]. Importantly, current therapies do not directly address inflammation, immune dysfunction, metabolic adaptation, and vascularization. Treatment is therefore guided by symptoms, lesion location, reproductive goals, and tolerability rather than molecular biomarkers. These limitations highlight the need for fertility-compatible, nonhormonal, lesion subtype-specific, and biomarker-guided therapies.

Emerging mechanism-based therapeutic strategies

Hypoxia activates YAP1, which induces inflammatory, steroidogenic, angiogenic, and lymphangiogenic mediators, whereas IL-1β further enhances COX-2 expression and PGE_2 production. PGE_2 impairs macrophage phagocytosis and induces the production of IL-6 to suppress NK-cell cytotoxicity. Inhibiting YAP1 or COX-2-PGE_2 signaling may therefore not only directly suppress lesion growth but also partially restore innate immune surveillance by enhancing macrophage-mediated clearance and reducing IL-6-mediated NK-cell dysfunction. However, these

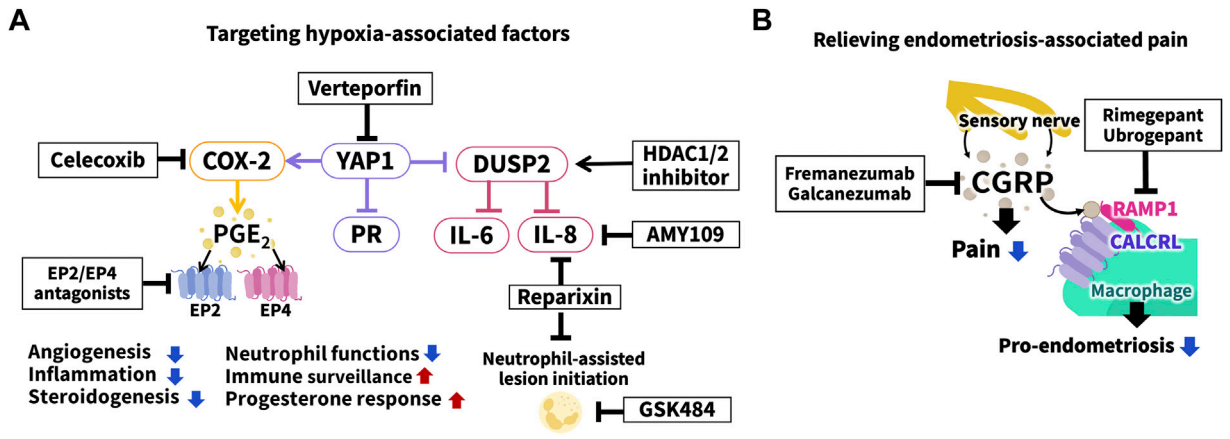


FIGURE 5
Emerging mechanism-based therapeutic strategies for endometriosis. Celecoxib and EP2/EP4 antagonists inhibit COX-2–PGE_2 signaling, whereas verteporfin inhibits YAP1, potentially reducing angiogenesis, inflammation, and steroidogenesis while restoring immune surveillance and progesterone responsiveness. HDAC1/2 inhibition may restore DUSP2, while AMY109 and reparixin suppress IL-8 signaling and GSK484 inhibits neutrophil extracellular trap formation. For relieving endometriosis-associated pain, Fremanezumab and galcanezumab neutralize sensory nerve-derived CGRP, whereas rimegepant and ubrogepant block the CALCRL–RAMP1 receptor complex, reducing pain and pro-endometriotic macrophage activity. Black T-shaped lines indicate inhibition; blue and red arrows indicate reduction and restoration, respectively. Abbreviations: CALCRL, calcitonin receptor-like receptor; CGRP, calcitonin gene-related peptide; COX-2, cyclooxygenase-2; DUSP2, dual-specificity phosphatase 2; EP2/EP4, prostaglandin E_2 receptors 2 and 4; HDAC1/2, histone deacetylases 1 and 2; IL-8, interleukin-8; PGE_2, prostaglandin E_2; PR, progesterone receptor; RAMP1, receptor activity-modifying protein 1; YAP1, Yes-associated protein 1.

immunomodulatory effects require direct experimental validation. ANTXR2 promotes stromal-cell adhesion and YAP1 activation. In mice, pharmacological ANTXR2 inhibition prevented lesion formation and reduced established lesion burden [24], raising the possibility that it could limit lesion growth and postoperative recurrence. In mouse models, verteporfin-mediated YAP1 inhibition reduced PGE_2 and estradiol production, angiogenesis, and lesion growth. It also restored progesterone receptor expression and decidualization in ectopic stromal cells, while combined verteporfin and dienogest treatment produced greater lesion regression than either treatment alone [101, 102]. These preclinical findings suggest that YAP1 inhibition may suppress lesion progression and improve responsiveness to progestins (Figure 5A). However, verteporfin is clinically used as a photosensitizer rather than as a selective YAP1-directed therapy. The development of more selective YAP inhibitors, together with evaluation of their reproductive and long-term safety, will therefore be necessary before this strategy can be translated clinically.

Restoring negative regulators suppressed by hypoxia represents another potential strategy (Figure 5A). Hypoxia-mediated downregulation of DUSP2 prolongs ERK and p38 MAPK activation, thereby amplifying IL-1β-induced COX-2 expression and increasing the production of IL-8 and IL-6. These mediators promote angiogenesis, inflammation, stromal-cell proliferation, and resistance to apoptosis. In a mouse model, the CXCR1/2 inhibitor reparixin attenuated IL-8-dependent angiogenesis and lesion development [80]. More recently, in cynomolgus monkeys with surgically induced endometriosis, the long-acting anti-IL-8 antibody AMY109 reduced lesion volume, fibrosis, and adhesions. [108]. A phase 1 clinical trial of AMY109 was conducted, and the results supported short-term safety and tolerability in humans [109]. These findings provide early translational support for targeting IL-8 signaling. Beyond angiogenesis, in mouse models, CXCR2 blockade reduced peritoneal neutrophil recruitment and early endometrial-tissue adhesion, suggesting that this approach may also prevent neutrophil-assisted lesion initiation [45]. Targeting neutrophil effector function provides another potential strategy. In mice, the peptidylarginine deiminase 4 inhibitor GSK484 suppressed NETosis, thereby reducing endometrial-tissue attachment and lesion development [110]. Restoring DUSP2 itself may provide a more upstream approach. Selective HDAC1/2 inhibition restored DUSP2 expression and function in colon cancer and in pancreatic ductal adenocarcinoma [111, 112], raising the possibility that epigenetic reactivation of DUSP2 could suppress multiple downstream pathways in endometriosis. However, this strategy has not been tested in endometriotic cells or animal models, and the broad transcriptional and reproductive effects of HDAC inhibition require careful evaluation.

The COX-2-PGE_2 pathway may be targeted using selective COX-2 inhibitors or EP-receptor antagonists (Figure 5A). In mice, celecoxib reduced lesion growth and vascularization [113, 114], whereas combined EP2/EP4 antagonism suppressed inflammation, angiogenesis, innervation, pain, and lesion growth [115]. However, PGE_2 is also essential for ovulation, implantation, and decidualization. In the eutopic endometrium, ciliary EP4 signaling activates the cAMP-PKA-CREB pathway required for decidualization [116, 117]. Systemic COX-2 or EP4 inhibition may therefore impair fertility and may be more suitable for patients not actively attempting pregnancy.

Angiogenesis and lymphangiogenesis provide additional therapeutic targets because lesions depend on vascular support, while lesion-associated lymphangiogenesis may facilitate immune-cell recruitment and sustain inflammation (Figure 5A). Inflammation-induced, extracellular vesicle-associated VEGF-C activates VEGFR2/VEGFR3 signaling in lymphatic endothelial

cells. In mice, the multikinase inhibitor Lenvatinib reduced lesion size, lymphatic-vessel density, lymph-node enlargement, and immune-cell infiltration [15]. Targeting blood-vessel formation may restrict the delivery of oxygen and nutrients to lesions. In a rat model of surgically induced endometriosis, bevacizumab, a monoclonal antibody that neutralizes VEGF-A, reduced lesion area after 4 weeks of treatment [118]. Although bevacizumab and Lenvatinib are FDA-approved for cancers, neither is approved for endometriosis. Systemic inhibition of VEGF signaling can impair physiological angiogenesis, wound healing, ovarian and endometrial function, and embryonic development. Accordingly, further studies are required to determine the clinical utility and reproductive safety of antiangiogenic strategies in endometriosis.

Relieving pain is central to improving the quality of life of women with endometriosis (Figure 5B). NGF is a key neurotrophic mediator that promotes sensory innervation of ectopic lesions. In mice, NGF neutralization and the pan-Trk inhibitor entrectinib reduced mechanical hypersensitivity and spontaneous pain-related behaviors [119]. The CGRP–RAMP1 axis provides another opportunity for drug repurposing, as all four agents tested in mice are FDA-approved migraine therapies (Figure 5B) [120]. Fremanezumab and galcanezumab are anti-CGRP monoclonal antibodies used for migraine prevention, whereas rimegepant and ubrogepant are orally administered small-molecule antagonists described in the study as targeting RAMP1. Rimegepant is approved for both acute treatment and prevention of migraine, whereas ubrogepant is approved for acute treatment. All four agents reduced mechanical hypersensitivity and spontaneous pain-related behaviors in mice, while rimegepant and ubrogepant additionally reduced lesion size; none significantly reduced lesion number [120]. These preclinical findings support further investigation of neuroimmune pathway inhibition as a potential therapeutic strategy. Overall, most of these emerging strategies are supported primarily by preclinical evidence, and their clinical efficacy and reproductive safety require further evaluation.

The mechanisms discussed above are unlikely to contribute equally across all forms of endometriosis, and their relative importance may vary according to lesion type, anatomical location, disease stage, and clinical phenotype. For example, subtype-specific studies have reported prominent mesothelial remodeling and lymphangiogenesis in deep endometriosis, while vascular, lymphatic, and immune alterations have also been described in peritoneal lesions. However, many mechanistic studies do not directly compare lesion subtypes, and the relative contribution of these pathways across different phenotypes remains unclear. Accordingly, emerging mechanism-based therapies should not be regarded as interchangeable treatments for all patients with endometriosis. For ovarian endometriomas, preservation of ovarian reserve is an important therapeutic consideration. In other phenotypes, dominant features such as vascularization, inflammation, or pain may help guide the selection of potential therapeutic targets. Biomarkers such as nuclear YAP1, PGE_2, IL-8, VEGF-C, and immune or neurotrophic signatures may help identify patients most likely to benefit from specific treatments, but they require clinical validation. Treatment strategies may also need to consider local, intermittent, or sequential approaches to minimize unwanted effects on ovulation, implantation, immune function, and tissue repair. Future studies should assess pain relief, fertility outcomes, disease recurrence, and long-term reproductive safety in addition to lesion regression.

Discussion

Despite substantial advances in understanding lesion establishment, immune dysfunction, metabolic adaptation, infertility, and pain, the cellular heterogeneity and causal mechanisms underlying these processes remain incompletely defined. Future studies should integrate scRNA-seq, spatial, epigenomic, proteomic, artificial intelligence-assisted methodologies, and metabolomic approaches to better characterize the molecular heterogeneity of endometriosis and translate mechanistic discoveries into clinically useful biomarkers [121–124]. Proteomic profiling of blood, menstrual effluent, and extracellular vesicles may facilitate the identification of non-invasive biomarkers for diagnosis, lesion classification, disease monitoring, and prediction of treatment response. However, the heterogeneity of extracellular vesicle populations in cellular origin and molecular cargo, together with differences in isolation and characterization methods across studies, remains an important challenge for their development as reproducible biomarkers. In parallel, scRNA-seq and spatial multi-omic analyses can resolve lesion subtype-specific cell states, intercellular communication networks, and the spatial distribution of endometrial, immune, vascular, fibrotic, and neural populations. Integrating transcriptomic data with epigenomic, proteomic, and metabolomic measurements may help distinguish transcriptional associations from downstream molecular changes and prioritize candidate pathways for functional validation.

These candidate mechanisms should be functionally validated using endometrial organoids, assembloids, and microphysiological models. Recent advances in endometrial assembloids [125], which integrate hormone-responsive epithelial and stromal compartments, provide a physiologically relevant platform for recapitulating key features of endometrial tissue. These models could be further adapted to reproduce distinct anatomical contexts of endometriosis. Mesothelial cells could be incorporated to investigate peritoneal attachment and invasion, ovarian stromal cells to model ovarian endometrioma formation, and intestinal epithelial and stromal cells to study deep bowel endometriosis. Such multicellular models would enable causal testing of candidate pathways through genetic or pharmacological perturbation and facilitate the evaluation of mechanism-based therapeutic strategies in tissue-specific microenvironments. Immune cells, including macrophages, NK cells, and T cells, can also be incorporated to recreate inflammatory and immunosuppressive microenvironments. These models could then be used to determine whether specific immune-cell states influence lesion establishment, stromal-cell behavior, and responses to immunomodulatory therapies. Such models may enable longitudinal analysis of lesion establishment, progression, and therapeutic response. Disease-associated complications could also be modeled directly. Embryo-like structures or blastoids co-cultured with endometrial assembloids may clarify how endometriosis impairs decidualization, implantation, and early embryo-maternal communication. In parallel, co-culture with sensory neurons may provide a platform

for investigating lesion innervation and pain-related mechanisms. Importantly, patient-specific assembloids generated from the endometrial tissue of women with endometriosis could be used to investigate individual disease mechanisms and test responses to candidate drugs *ex vivo*. Linking patient-specific molecular profiles with *ex vivo* drug responses may help identify patient subgroups with differential treatment responses, thereby supporting treatment stratification and personalized therapeutic strategies. However, standardization of sample collection, culture conditions, cellular composition, and clinically relevant readouts will be required before these technologies can support biomarker validation or precision treatment.

Author contributions

S-JT, M-HW, and H-TH conceived the review, conducted the literature search, drafted the manuscript, and prepared the figures. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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