Molecular mechanisms underlying the inhibition of cell migration and invasion in endometriosis: Advances in pharmacological research (Review)

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Abstract. Endometriosis (EMS) is a prevalent gynecological disease afflicting reproductive-age women, characterized by the presence of endometrial tissue outside the uterus. The clinical manifestations of this condition include pelvic pain, dyspareunia, and, in severe cases, infertility. The pathology of EMS is similar to that of malignant tumors in terms of implantation, invasion and metastasis, which complicates diagnosis and treatment. Ectopic endometrium has the potential to invade the ovaries, the uterosacral ligament, the peritoneum, and the vaginal wall. Its core mechanism involves the dynamic regulation of cell migration and invasion, which is an important process affecting the development and distant metastasis of EMS. Therefore, understanding the underlying mechanisms of its formation and development is crucial for its treatment. At present, research on inhibitors targeting such mechanisms remains in the exploratory stage and has yet to be translated into clinical applications. The present study aimed to methodically review the molecular regulatory network of cell migration and invasion in EMS, encompassing the interactions between relevant cells, the functions of key signaling pathways, and regulatory factors. The authors focused on chemically synthesized drugs, plant extracts, Chinese medicine, potential targets of action and mechanisms. The present review offers novel research concepts and theoretical foundations that may facilitate the identification of novel therapeutic targets for EMS. These targets could be implemented in clinical settings to effectively mitigate metastasis and recurrence rates, thereby enhancing our comprehension of the intricacies of the disease, and guiding the exploration of more efficacious therapeutic avenues.

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Abbreviations: EMS, endometriosis; BC, breast cancer; ECM, extracellular matrix; EECs, endometrial epithelial cells; ESCs, endometrial stromal cells; EESCs, ectopic ESCs; EMT, epithelial-mesenchymal transition; EuESCs, eutopic ESCs; HESCs, human ESCs; ILK, integrin-linked kinase; JNK, Jun N-terminal kinase; OC, ovarian cancer; PMCs, peritoneal mesothelial cells; TCM, traditional Chinese medicine; TNF, tumor necrosis factor; MMP, matrix metalloproteinase

Key words: EMS, migration, invasion, therapeutic drugs, signaling pathways, targeted therapy

Contents

1. Introduction

Endometriosis (EMS) is a chronic inflammatory gynecological disease characterized by the invasive growth of ectopic endometrial tissue outside the uterine cavity. The clinical manifestations of EMS include severe dysmenorrhea, menstrual abnormalities and fertility disorders (1). Epidemiologic data (1,2), show that ~30-50% of patients with EMS have fertility disorders, while 50-80% of cases of pelvic pain are associated with the disease, which has a global prevalence of more than 176 million. However, the absence of specific biomarkers and the presence of non-specific clinical symptoms in the early stages of the disease often result in delayed or misdiagnosis (3), which can lead to suboptimal treatment outcomes and a recurrent course of pain.

In 1986, Sanfilippo *et al* (4) proposed that the primary causative factor of EMS is reversal of menstrual blood flow, and the disease is now regarded as systemic, rather than one that is primarily confined to the pelvis (1). The classification of EMS is based on its location and severity, with three distinct forms: superficial, ovarian and deep infiltrative (5), as shown in Fig. 1. The heterogeneity of EMS across different subtypes is a significant factor contributing to the challenges associated with the development of effective medication. Furthermore, the development of EMS may be influenced by a variety of factors, including geographic location (6), ethnicity (7), genetics (8), lifestyle and dietary habits (9).

The etiology of endometriotic lesions remains a subject of considerable debate, with several theories proposing potential mechanisms, including retrograde menstruation, cellular chemotaxis, involvement of stem cells, blood or lymphatic dissemination, and the theory of embryogenesis introduced by Burney and Giudice (10). Among the various mechanisms, cells may require the capacity to migrate, invade, and adapt to new microenvironments, and studies have demonstrated that cell migration and invasion are of paramount importance in this context (11-13). However, it is imperative to acknowledge the interplay between cells associated with EMS, such as endometrial stromal cells (ESCs), endometrial epithelial cells (EECs), immune cells and stem cells, among others (14-18). Studies (19,20) have confirmed the migration, invasion, epithelial-mesenchymal transition (EMT) and inflammation of the relevant cells through *in vitro* experimentation, thereby providing a foundation to predict the therapeutic effect.

Another study (21) elaborated on the pathogenesis of related molecules in EMS by regulating the proliferation and migratory activity of ESCs. Estrogen signaling plays a central regulatory role in the remodeling of the disease microenvironment. For instance, 17β-estradiol influences lesion progression by modulating the expression levels of inflammatory factors (22). The signaling pathways associated with migration and invasion of EMS cells, as well as their upstream and downstream regulators, constitute a large and complex transduction system. Abnormalities in these pathways and their interactions can lead to abnormal proliferation, apoptosis, migration, invasion, angiogenesis, immune system, and inflammatory responses in ectopic endometrial tissues, resulting in rapid proliferation of lesions. In this process, matrix metalloproteinases (MMPs) (23), adhesion molecules (24), small-molecule proteins (25) and hormone receptor systems (26) play important roles. The process of cell migration and invasion is influenced by the dysregulation of downstream molecules, such as MMPs and adhesion molecules, due to localized inflammation and immune responses within the cellular microenvironment.

The prevailing treatment for EMS is primarily surgical resection, followed by the postoperative administration of gonadotropin-releasing hormone agonist (GnRH-a) (27). However, it is improbable that pharmacologic therapy will fully attenuate the cells. The primary adverse effects associated with prolonged GnRH-a administration are perimenopausal symptoms and hypoestrogenic-induced osteoporosis (28), and some patients may also encounter severe bone pain.

With the advent of molecular targeted therapy and gene editing technology, precision diagnostic systems and gene therapy (29) based on blood microRNA (miRNA or miR) biomarkers (30) have gradually become a research focus. miR-193b-5p and miR-374b-5p can inhibit endometrial cell migration in *ex vivo* experiments (31). KLF6 is a tumor suppressor gene (32), and overexpression thereof significantly inhibits ECESC proliferation, migration and invasion, as well as induces cell apoptosis in eutopic ESCs (EuESCs) and ectopic ESCs (EESCs) knockdown and overexpression assays (33).

Current research has focused on the exploration of the mechanisms of natural drug active ingredients. For example, a recent study by Meng *et al* (34) investigated the anti-EMS mechanism of the classic Chinese herbal medicine formula Juan-Tong-Yin. It was found that the formula could improve the inflammatory microenvironment by enhancing endoplasmic reticulum stress and autophagy, and decreasing the migration and invasion of ESCs to treat EMS (35).

The molecular mechanisms associated with EMS cell migration and invasion, as well as drug studies, are crucial for clinical treatment. It was therefore aimed to review the mechanisms of action and risks of these drugs to develop more effective treatments for EMS.

2. Mechanisms of EMS cell migration and invasion

Although a number of studies have been devoted to unraveling the pathogenesis and treatment of EMS, its pathophysiology and molecular mechanisms are still not fully understood. Cell migration and invasion are important factors in the pathogenesis thereof and are important processes that promote the formation and growth of ectopic endometrial tissues, with mechanisms involving the regulation of cell adhesion molecules, MMPs, extracellular matrix (ECM) remodeling, the hypoxic microenvironment and mesenchymal transition, among other factors.

Anti-cell migration and invasion mechanism. The development and progression of EMS is dependent on the migration and invasion of endometriotic cells (36), as shown in Table I (37-40). An increasing number of researchers are judging the effectiveness of intervention components by studying the migration and invasion abilities of EMS cell models, and through continuous development, the research direction is gradually moving toward non-invasive biomarker screening, the establishment of *in vivo* animal models, the study of related signaling pathways, and the prospective treatment with targeted drugs.

Table I. Inhibitory effects on cell migration and invasion across different tumor types.

First author/s, year	Tumor	Mechanism	Impact	Target	(Refs.)
Mao *et al*, 2019	CC	CSN6 promotes the migration and invasion of CC cells by inhibiting autophagic degradation of Cathepsin L	Highly lethal and aggressive	CSN6	(37)
Gao *et al*, 2020	OC	MiR-26a inhibits ovarian cancer cell proliferation, migration and invasion by targeting TCF12	Survival and poor prognosis	TCF12	(38)
Geng *et al*, 2021	EC	MiR-29a-3p inhibits EC cell proliferation, migration and invasion by targeting VEGFA/CD C42/PAK1	Tumor metastasis, invasion and poor prognosis	miR-29a-3p	(39)

OC, ovarian cancer; EC, endometrial cancer; CC, cervical cancer; miR, microRNA.

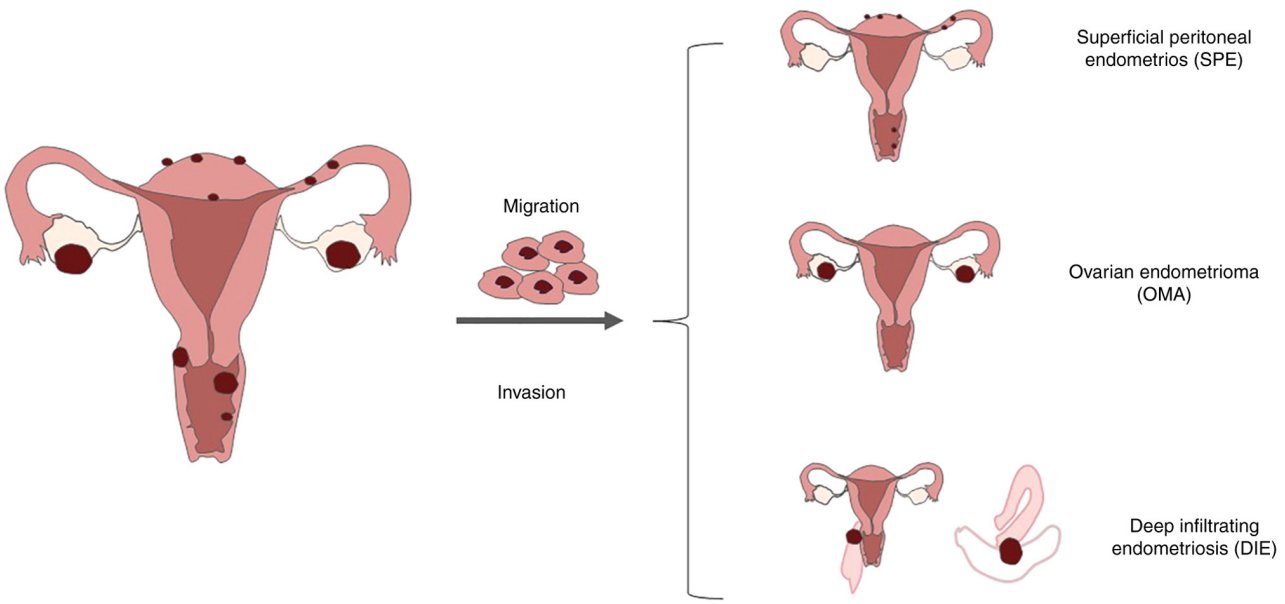


Figure 1. Endometriosis can take one of three forms depending on its clinical presentation and management: OMA, SPE, DIE. OMA, ovarian endometrioma; SPE, superficial or peritoneal endometriosis; DIE, deep infiltrating endometriosis.

Cellular characterization of EMS. The pathological evolution of EMS is closely related to cell migration, adhesion, invasive behavior, dynamic remodeling of the cytoskeleton, microenvironmental remodeling, and the EMT process, which involves interactions between multiple cell types. Among them, ESCs, as core effector cells, can be ectopically implanted and initiate lesion formation via the transepithelial reflux pathway. ESCs from patients with EMS present a unique pathological phenotype when interacting with peritoneal mesothelial cells (PMCs). This includes the upregulation of adhesion molecule expression to enhance the anchoring ability of the cells, the aberrant mesenchymal marker expression driving EMT progression, invasive pseudopod formation, and increased secretion of matrix degrading enzymes, as well as more invasive and motile ESCs promoted by PMCs (14,15). ESCs from patients with EMS exhibit significant changes in mechanical properties, such as reduced cell deformability and stiffness, which makes these cells susceptible to migration and spreading in the microenvironment (41).

Additionally, diseased ESCs often show myofibroblast-like transformation accompanied by α-SMA overexpression and increased collagen secretion, and their pro-fibrotic features have molecular similarities with tumor microenvironment (TME) remodeling (42). As shown in Fig. 2, the peritoneal cavity immune network exhibits multicellular synergistic features, with macrophages amplifying local inflammation through CCL2/CXCL1-mediated neutrophil recruitment, which promotes the proliferation and migration of EESCs (16,17). NK cells secrete IFN-γ to regulate Th1/Th2 balance, and dendritic cells activate T-cell immune responses through MHC-II-mediated antigen presentation (43-46). Mast cells are also involved in the immune and inflammatory response therein through recruitment and differentiation, secretion of pro-inflammatory mediators (47,48). A recent study (49) identified a novel class of 'Pale cells', which lack

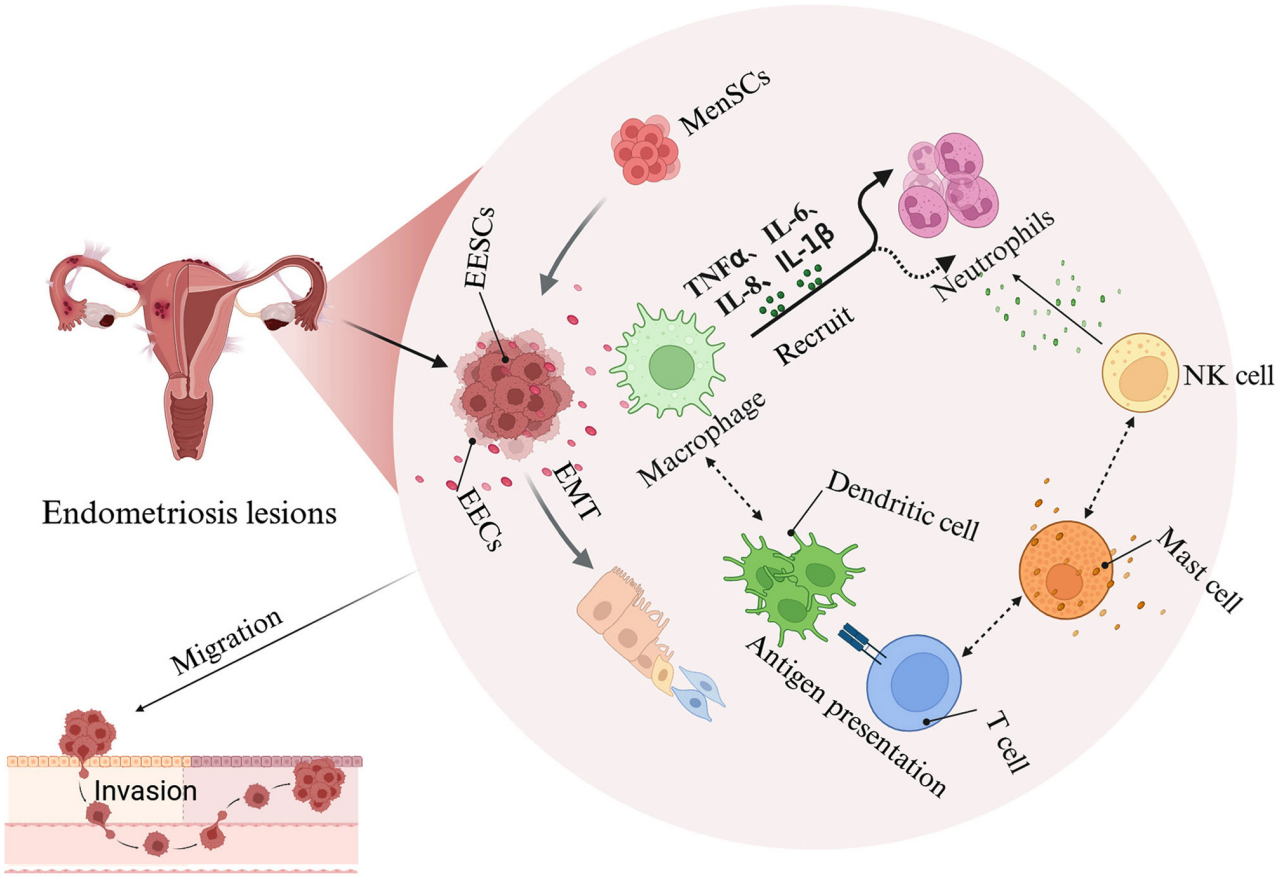


Figure 2. Regulatory map of cellular interactions during endometriosis cell migration and invasion. EESCs, ectopic endometrial stromal cells; EECs, endometrial epithelial cells; NK cell, natural killer cell; EMT, epithelial-mesenchymal transition; MenSCs, menstrual blood-derived stem cells.

bridging granule structures and have a translucent cytoplasm, and may be involved in migration and invasion, but the lack of *in vitro* culture models prevents further investigation.

Menstrual blood-derived stem cells exhibit abnormal homing ability and paracrine dysfunction in patients with EMS, and exhibit different properties in patients with EMS, which may be biomarkers for early diagnosis and treatment (18). Taken together, the cellular heterogeneity and multicellular interaction network of EMS provide key entry points to analyze the pathogenesis and develop targeted intervention strategies.

PI3K/Akt/p-mTOR pathway. The ability of EMS cells to migrate and invade is a central pathological feature driving lesion development, progression and ectopic dissemination. The molecular mechanism involves a complex cascade of abnormalities in the function of the resident endometrial stem cells, interactions of multiple molecular networks, and dynamic regulation of the microenvironment. Cellular and molecular studies have shown that a variety of proteins, genes, and compounds can regulate the process of cell migration and invasion by activating specific signaling pathways. As a heterodimer with serine/threonine kinase activity, phosphatidylinositol 3-kinase (PI3K) plays a key role in the regulation of cell migration and invasion by collaborating with protein kinase B to form a classical signal transduction axis. A typical example is DJ-1 protein, which promotes endometrial cell proliferation, migration, and angiogenesis by activating the PI3K/Akt/p-mTOR signaling cascade, suggesting its potential value as a common therapeutic target for EMS and adenomyosis (50).

Immunoglobulin superfamily member 8 (IGSF8), known as EWI-2, inhibits endometrial cell proliferation, invasion and filamentous pseudopod formation by negatively regulating the Akt signaling pathway (51,52). Zheng and Yang (53) demonstrated by protein blotting analysis that knockdown of EWI-2 could significantly enhance the level of Akt phosphorylation, which promotes the migratory invasion ability of EECs, revealing a critical negative regulatory role of the EWI-2-PI3K/Akt axis in EMS. These gene-level-based studies may provide new directions and further ideas for subsequent research strategies.

In addition, the plant-derived flavonoid 3,6-dihydroxyflavone exerts anticancer effects by inhibiting pathological processes such as malignant transformation and invasion of tumor cells (54,55). This compound significantly reduces the migratory invasive ability of ESCs by inhibiting the expression of key effector molecules of the Notch signaling pathway (56). *In vitro* assays have demonstrated that the PI3K/Akt pathway agonist 740 Y-P effectively reverses the effects of GATA-binding protein gene silencing on the proliferation, migration and death of EESCs (57). A mechanistic analysis has also revealed that PGRN overexpression significantly elevates the p-Akt/Akt ratio, while the PI3K inhibitor LY294002 completely blocks the promotion of PGRN on ESC

proliferation and invasion (58). Further studies are needed to develop antibody therapy to block EMS and improve targeting efficiency.

Wnt/β-catenin and NF-κB pathways. The wingless-type mouse mammary tumor virus integration site family (Wnt) signaling axis plays a critical role in regulating EMS cell migration and invasion. The silencing of the multidrug resistance protein 4 gene can contribute to the progression of endometrial lesions by inducing aberrant activation of Wnt/β-catenin signaling (59). The downstream effector molecules of this pathway, MMP-2/-9 and cyclin D1, are significantly overexpressed in EECs and ESCs of patients with EMS (60).

The MMP family, a group of key effector molecules, has also been shown to regulate cell migration, invasion and angiogenesis through the modulation of growth factor/cytokine dynamics. Abnormally high expression of MMPs is positively correlated with the pathological progression of EMS (61). Furthermore, T-cell factor/β-catenin (Tcf/β-catenin) complexes can transcriptionally inhibit MMP-9 activity and restore cell invasion ability to normal endothelial levels, suggesting their potential value as therapeutic targets for EMS (62). However, the field of EMS research has yet to dedicate significant resources to this topic.

NF-κB is a class of key proteins that can significantly drive the cell proliferation process while effectively inhibiting the apoptosis phenomenon in endometrium and endometriotic cells. In 2018, Li *et al* (63) identified an oncogene, programmed cell death 4, which inhibits cell proliferation by suppressing autophagy and the NF-κB/MMP2/MMP9 signaling pathway, thereby inhibiting endometrial cell proliferation, migration and invasion. This jointly inhibits disease progression at the transcriptional and translational levels.

Effect of the cellular microenvironment

Hypoxic microenvironment. The hypoxic microenvironment is an important factor affecting EMS cell proliferation and invasion, promoting ESC migration and invasion by upregulating autophagy. Autophagy is an intracellular process of protein and organelle degradation that is mediated through lysosomes, with the primary function of maintaining stability of the intracellular environment (64). In the physiological state, the process is cytoprotective; however, excessive activation or dysfunction of autophagy can lead to organelle depletion and induce programmed death (65-67).

Preliminary experimental studies have demonstrated that treatment with hypoxia results in enhanced migration of EECs, concurrently inducing autophagy, thereby activating the EMT process (68). Mechanistic elucidation (69) has revealed that hypoxia promotes the formation of autophagic vesicles by stabilizing hypoxia-inducible factor-1α (HIF-1α), which drives the invasive phenotype of EESCs. Paeonol intervention inhibits this process in a dose-dependent manner, downregulating the LC3-II/LC3-I ratio, and upregulating p62 expression. This ultimately restores the migratory capacity of EESCs to normoxic levels. The HIF-1α/autophagy signaling axis amplifies the invasive potential of EMS foci through a positive feedback loop (70).

In a recent study, a network pharmacology *in vitro* and *in vivo* model demonstrated that the Chinese herbal compound 'Luoshi Neiyi prescription' significantly inhibited endometrial stromal cell adhesion and invasion by targeting the HIF1A/EZH2/ANTXR2 signaling axis (71). Hypoxia promotes EEC invasion (68), and the initial events that are critical in the formation of EMS lesions are initiated by cellular responses to hypoxic conditions, which subsequently activate the autophagy cascade effect. This activation drives the process of EMT while enhancing the invasive potential of endometriotic cells (72).

Furthermore, the hypoxic microenvironment plays a pivotal role in the migration and invasion of tumor cells, with the process being regulated by carbonic anhydrase IX (CAIX)-mediated pH dynamics (73). The functional significance of CAIX in tumor cell migration and invasion has been well-established; however, its potential applications in the context of EMS cell migration and invasion remain to be elucidated. Consequently, the concerted targeting of the hypoxia-autophagy-EMT regulatory network may emerge as a novel therapeutic strategy for the treatment of EMS.

EMT. EMT is a complex event that drives the transformation of polarized epithelial cells from adherent cells to motile mesenchymal cells. This process involves immune cells and stromal cells, and EMT plays a crucial role in migration and invasion in EMS (74). During the process thereof, cells undergo a series of significant changes, including the loss of cell polarity; attachment to the basement membrane; enhanced invasion, migration, anti-apoptosis; and ECM degradation; as well as a decrease in cell adhesion (75). Aberrant activation of the oncogenic signaling pathway, the presence of hypoxia, and the interactions with stromal cells are crucial factors that contribute to the process of EMT. This leads to a decrease in intercellular adhesion and an enhancement in migratory and invasive phenotypes (76).

EMT is more active in non-endometriotic tissues compared with ectopic endometriotic tissues (77). The novel findings of Liu *et al* (68) suggest that hypoxia-induced activation of autophagy cascades is central to the invasive phenotypic profile of EMT and endometriotic implant cells. They also found that the interaction between endometriotic implants and the surrounding peritoneal microenvironment may influence the endometrial microenvironment. These interactions exert a significant influence on the development of peritoneal EMS, and it was sought to explore the classification of EMT for the purpose of facilitating a more precise diagnosis and treatment of peritoneal EMS.

EMS and malignant neoplasms, including ovarian cancer (OC) and breast cancer (BC), exhibit significant similarities at the level of molecular mechanisms, such as autophagy regulation, EMT processes and ECM remodeling. The transition from an epithelial to a mesenchymal phenotype is associated with systemic dissemination of cells from the primary site, which significantly enhances the migration and invasion of tumor cells (78). Transmembrane protein 176B can effectively block the EMT process by inhibiting the activation of the Wnt/β-catenin signaling pathway, which inhibits OC cell migration, invasion and adhesion (79). Complementary evidence based on *ex vivo* and *in vivo* experiments has shown that lysine acetyltransferase 2B gene silencing enhances autophagic activity through activation of the TGF-β/Smad3/7 signaling pathway, which drives the EMT-dependent proliferative and invasive phenotypes of epithelial OC (80).

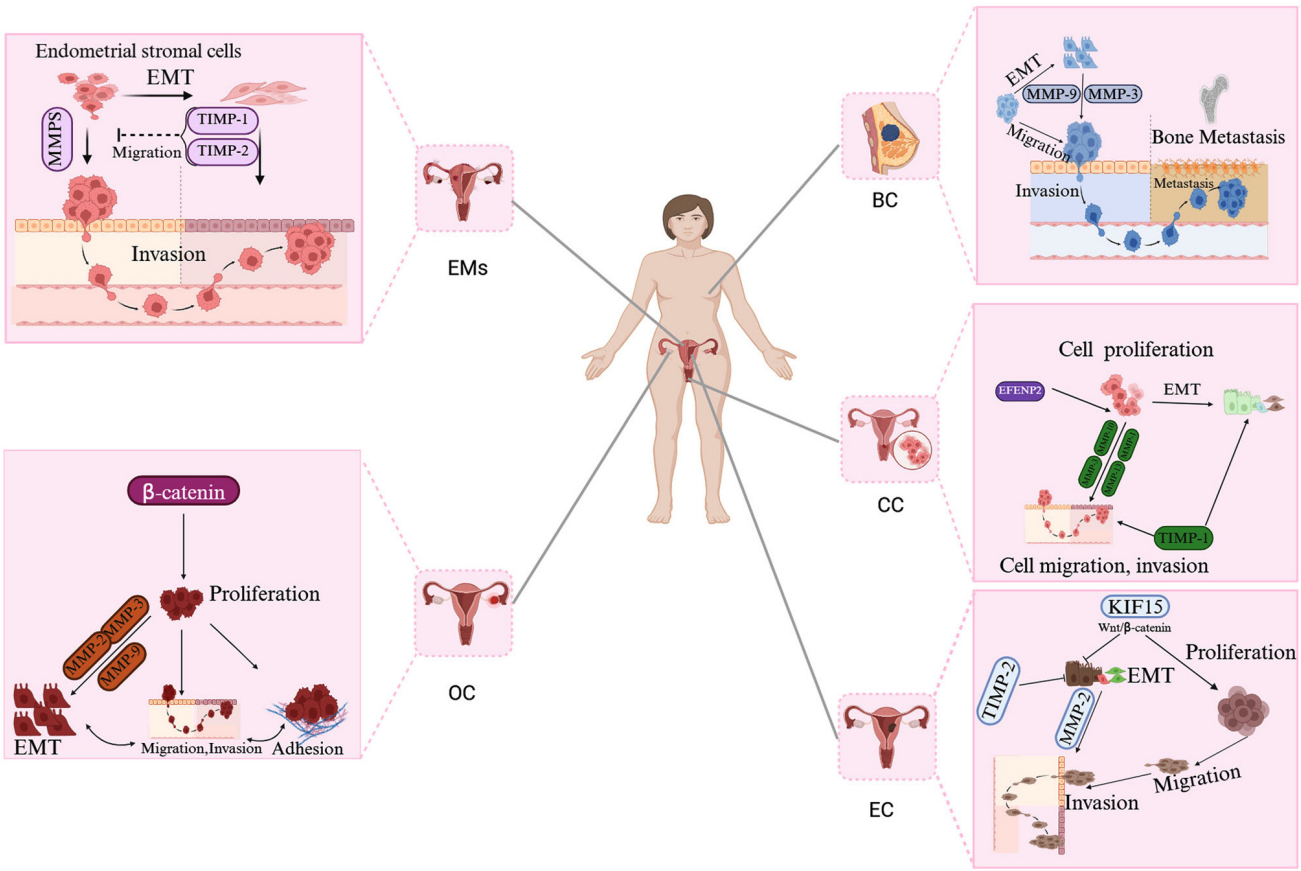


Figure 3. Mechanisms of action of related EMT and MMPs in EMS, OC, BC, CC and EC. EC, endometrial cancer; BC, breast cancer; OC, ovarian cancer; CC, cervical cancer; EMT, epithelial-mesenchymal transition; MMP, matrix metalloproteinase; EMS, endometriosis; TIMP, tissue inhibitors of metalloproteinase.

In endometrial cancer (EC) studies, kinesin family member 15 knockdown significantly inhibited the EMT process by suppressing Wnt/β-catenin signaling, thereby reducing tumor cell proliferation, cloning, migration and invasive capacity (81). A study based on preclinical models and pre- and post-treatment biopsy samples from patients with EC confirmed that systemic application of an anti-netrin-1 antibody significantly reduced the expression of EMT signature markers in tumor cells and increased chemosensitivity (82). Although the molecular mechanisms by which EMT regulates the malignant phenotype of tumors have been thoroughly analyzed, clinical interventions targeting the EMT process are still extremely limited, and the clinical trial conducted by Cassier *et al* (82) is the first to systematically evaluate antitumor strategies targeting the EMT signature, providing an important paradigm for translational medicine research.

Mechanisms related to cervical cancer (CC) have shown that EFEMP2 gene silencing can significantly inhibit cancer cell proliferation and invasion by synergistically downregulating MMP-1/3/10/13 expression, blocking EMT progression, and inhibiting the Raf/MEK/ERK signaling pathway (83). Conversely, EFEMP2 overexpression promoted tumor progression by inducing EMT and activating the Raf/MEK/ERK signaling pathway (83). Similarly, the metastatic process of BC was found to be closely associated with EMT-mediated dysregulation of MMP-9/13 expression (84). As demonstrated in Fig. 3, a comprehensive review of the existing literature revealed that the mechanisms of EMT associated with EMS and the female reproduction-related cancers (OC, EC, CC and BC) were analogous. A comparative analysis of the EMT features of EMS and cancer revealed numerous commonalities, particularly with regard to MMPs.

Future studies should systematically elucidate the multidimensional mechanisms by which the hypoxic microenvironment regulates the progression of EMS, with a focus on resolving the synergistic network of hypoxia-induced autophagy and EMT. It is recommended that the well-established EMT regulation strategies be integrated into tumor invasion research, and that a 'hypoxia-autophagy-EMT' cascade model be constructed by targeting the HIF-1α/PI3K/Akt signaling axis to intervene at the key nodes of EMT (for example, Snail, Twist1 and ZEB1). This research direction will facilitate the elucidation of the molecular foundations that govern the acquisition of invasive properties by ectopic endothelial cells. Moreover, this will provide a theoretical framework for the development of multi-targeted therapeutic strategies that are based on the inhibition of EMT.

Molecular mechanisms associated with cell migration and invasion in EMS. Abnormalities in the molecular mechanisms associated with cell migration and invasion result in persistent growth and inflammatory responses of ectopic endometrial tissue. The MMP family plays an important role in cell migration and invasion. In addition, RNA molecules are involved in the adhesion and migration of ectopic endometrial cells to the

Table II. MMPs associated with endometriosis progression: Mechanisms regulating cell migration and invasion.

First author/s, year	Types of MMP	Machine	Role	Reported elsewhere	(Refs.)
Sharpe-Timms *et al*, 1998	TIMP-1	Concentrations in peritoneal fluid and serum are lower in patients with endometriosis than in normal women	Diagnosing endometriosis and monitoring treatment outcomes	CC, EC	(86)
Wenzl *et al*, 1998	MMP-2	Endometriotic tissues express proteases capable of invading surrounding tissues	Localization in the uterine endometrium and ectopic implants	OC, EC, CC, BC	(87)
Cox *et al*, 2001; Lv *et al*, 2015	MMP-3	Ectopic endometrial MMP-3 may be involved in the process of invasion and tissue remodeling that occurs in the pathogenesis of endometriosis. miR-93 inhibits the proliferation, migration and invasion of endometrial stromal cells by combining MMP3 and VEGFA	Differential regulation of matrix metalloproteinase-3 gene expression in endometriotic lesions in comparison with endometrium, inhibition of endometriosis migration	OC, CC	(88,89)
Chung *et al*, 2002	TIMP-2	Expression levels are associated with endometriosis aggressiveness	Explain the aggressive factors leading to endometriosis	EC, CC	(90)
Collette *et al*, 2006; Lin *et al*, 2021	MMP-9	MMP-9/TIMP-1 imbalance is involved in tissue Invasion and Ectopic Development in patients with endometriosis. Cytokine IL-33 acts on stromal cells to promote cell invasion and MMP-9 expression in endometriosis	Supporting an important role for MMP-9 in the ability of endometrial tissue to invade and develop into host tissue. Providing new strategies for the prevention and treatment of endometriosis	OC, EC, CC, BC	(91,92)
Gaetje *et al*, 2007	MT5-MMP	MT5-MMP expression is significantly elevated in human endometrium and endometriosis lesions	Influence endometriosis invasion		(93)

TIMP, tissue inhibitors of metalloproteinase; MT5-MMP, membrane type 5 metalloproteinase; OC, ovarian cancer; EC, endometrial cancer; CC, cervical cancer; BC, breast cancer.

surrounding tissues. Further research is needed to investigate the role of cytokines, inhibitors, proteins and genes in this process. However, due to the intricate pathogenesis of EMS, as illustrated in Fig. 4, the research timeline concerning molecules implicated in the design of EMS migration and invasion, the prevailing treatment for EMS as a first-line drug therapy and the lack of molecularly-targeted drugs available for clinical application, make it necessary to consider the feasibility and effectiveness of molecular drugs.

MMPs associated with EMS cell migration and invasion. MMPs are a family of at least 15 secreted and membrane-bound zinc endopeptidases that degrade all components of the ECM, including fibrillar and nonfibrillar collagens, fibronectin, laminin, and basement membrane glycoproteins. MMPs are imperative for a range of invasive processes implicated in angiogenesis and tumor metastasis (85). Among these, MMP-2 and MMP-9 are key effector molecules, whose expression levels are significantly and positively correlated with the ectopic invasive ability of EMS, and the progress of the MMP family in EMS-associated migration and invasion, as shown in Table II (86-93).

Since the first discovery of stromelysin in endometrial tissues in 1993 by Rodgers *et al* (94) and the confirmation of MMP properties and pathological functions, the centrality of MMPs in the regulation of tissue remodeling and invasion in EC has been repeatedly substantiated. It has been demonstrated that L-33 enhances the invasive capacity of human ovarian endometriotic stromal cells by activating MMP-9 expression (92). Furthermore, miRNA-34a-5p exerts an inhibitory effect on the transcriptional activity of the MMP-2 gene by directly binding to its 3'-untranslated region, thereby significantly curtailing the invasive migratory capacity and stemness maintenance function of ESCs (23).

MMP-9 significantly enhances the invasive ability of endometriotic cells through degradation of basement membrane type IV collagen and activation of precursor growth factors, which are involved in the pathologic process of EMS. Tissue inhibitors of metalloproteinases (TIMPs), as endogenous regulatory proteins, can maintain the dynamic balance of degradation and synthesis of ECM through specific binding to the active site of MMPs (85). This suggests that targeted modulation of MMP-9 expression or enzymatic activity may

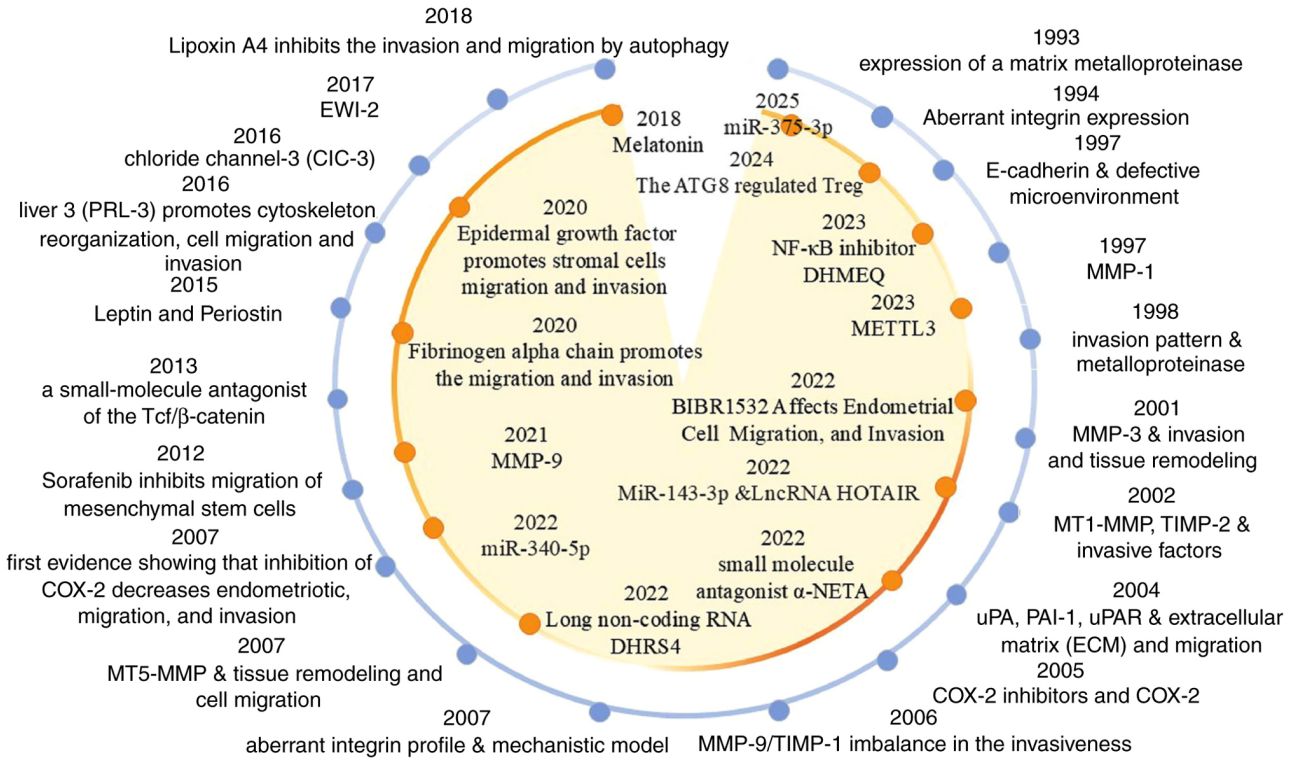


Figure 4. Timeline of molecular studies related to endometriosis cell migration and invasion. A timeline of the discovery and development process of molecules related to endometriosis cell migration and invasion is presented from the first discovery of MMPs in 1993 to the discovery of miR-375-3p in 2025. miR, microRNA; MMP, matrix metalloproteinase; TIMP, tissue inhibitors of metalloproteinase.

be a novel therapeutic strategy to inhibit cell migration and invasion. However, the translational application of TIMPs is severely limited due to their short half-life *in vivo* and systemic toxicity.

Imbalance of the MMPs/TIMPs ratio is not only a central feature of invasive metastasis in EMS, but also exists in benign diseases such as malignant tumors. Epidemiologic studies have shown that patients with EMS have an elevated risk of developing OC compared with the normal population (95,96). OC is a lethal gynecologic malignancy, and has a unique pattern of transcavitary metastasis, resulting in extensive implantation of cancer cells on the peritoneal and omental surfaces (97). EMS and OC show remarkable similarity in cell migration invasion mechanisms, and MMP14 (MT1-MMP), MMP2, and MMP9 can be activated through the synergistic degradation of ECM components such as laminin/fibronectin, activation of EMT, and upregulation of related transcription factors, which together drive the malignant dissemination of OC cells (97).

Clinicopathological analyses have shown that the expression levels of MMPs are generally upregulated in OC tissues compared with normal ovarian tissues (98). Conversely, inhibition of MMP activity reduces the progression of cell invasion *in vitro* and metastasis *in vivo* (99). Based on this, researchers have developed machine learning models integrating markers such as MMP-2/-3/-11/-26, HE4 and CA125, which have an area under the receiver operating characteristic curve of 0.97 for the diagnosis of OC (100).

Mechanistic studies have revealed that enhancing zeste homolog 2 (EZH2), a histone lysine N-methyltransferase, could enhance OC cell invasiveness by inhibiting TIMP2 expression to reduce and promote MMP9 transcription. The covalent EZH2 inhibitor SKLB-03220 reverses this effect and restores the TIMP2/MMP9 ratio to physiological levels (101). In addition, the invasive and metastatic process of BC, a highly prevalent malignancy in women, is also significantly dependent on MMP2/MMP9-mediated ECM remodeling (102).

High expression of MMP-2, together with low expression of TIMP2, suggests an increased risk of local and distant metastasis in EC, and both molecules have the potential to be key markers for human gynecological cancer cell lines (98). Furthermore, MMP9 may be a favorable marker for the adjuvant diagnosis of early EC (103).

In the pathological process of CC, MMP-2 drives malignant progression through a dual mechanism, directly degrading type IV collagen to disrupt basement membrane integrity; and regulating the MMP cascade and the dynamic balance of ECM components (cytokines, chemokines and growth factor receptors) (104). Shukla *et al* (104) compared patients with CC with healthy individuals and found that elevated serum MMP-2 levels were positively correlated with higher CC stage, and MMP-2 expression increased progressively with the grade of cervical intraepithelial neoplasia, peaking at the stage of CC. In a CC-related study, Schröpfer *et al* (98) demonstrated that CC cells (HeLa/Caski/SiHa) showed heterogeneity in MMP expression profiles by multicellular lineage analysis, with MMP-1/-11/-13/-15/-17/-24/-28 being commonly expressed in all three lines. Additionally, high expression of MMP-9 was associated with poor prognosis in CC, leading to a study conducted to inhibit the proliferation of human CC cells by reducing the expression of MMP-9 (105).

Table III. Differentially expressed RNAs associated with cell migration and invasion in endometriosis.

First author/s, year	Name	Mechanism	Experimental model	Role	(Refs.)
Lv *et al*, 2015	miR-93	Inhibits the proliferation, migration and invasion	ESCs	Therapeutic target	(89)
Frisendahl *et al*, 2024	miR-193b-5p and miR-374b-5p	Inhibits migration	The human immortalized epithelial endometriotic cell line (12Z) and the endometrial stromal cell line (HESC)	Explain the pathogenesis	(31)
Wan *et al*, 2022	hsa-miR-340-5p	Restrains migration, invasiveness and EMT	ESCs	Therapeutic target	(107)
Zhang *et al*, 2022	miR-30c	Diminishes the invasion and migration	Endometrial epithelial cells	Attenuating the tumor-like behaviors	(108)
Ntzeros *et al*, 2025	miR-1229-5p	MiR-1229-5p overexpression promotes migration, invasion, and inhibits apoptosis	ESCs and Ishikawa cells	Therapeutic target	(109)
Hagh *et al*, 2024	miR-2233p and miR-200a	Low expression	Secretory phase endometrium	Diagnostic biomarkers	(110)
Wang *et al*, 2025	miR-375-3p	Suppresses cell proliferation, migration, and invasion	Endometriosis cell line, hEM15A	Biomarker for EMs	(111)
Zhang *et al*, 2024	miR-145	Estrogen receptor α mediates stromal cell migration	Stromal cell	Therapeutic target	(112)
Cui *et al*, 2022	DHRS4	Inhibits EC-ESC proliferation, migration and invasion, but promotes apoptosis	Ectopic ESCs	Therapeutic target	(113)
Bao *et al*, 2022	HOTAIR	Inhibits the invasion and migration ability	ESCs	Mechanism study	(114)

ESCs, endometriosis stromal cells; miR, microRNA.

TIMPs and MMPs co-regulate the ECM remodeling process and are closely related to tumor growth, invasion and metastasis. They play a key role in regulating the activities of various enzymes in the ECM. The regulatory network of MMPs has universal biological significance in malignant invasive phenotypes, and TIMPs, as endogenous inhibitors of MMPs, are involved in the entire process of tumor growth and metastasis regulation by modulating the ECM enzyme activity network. MMP-9 overexpression in the TME can promote ECM remodeling and metastatic foci formation through degradation of basement membrane proteoglycan and activation of integrin signaling (106). As shown in Fig. 3, the interaction between MMPs and EMT is highly conserved in EMS and gynecological malignancies, and its synergistic regulatory network provides a molecular basis for the development of cross-disease therapeutic strategies.

RNAs associated with EMS cell migration and invasion. RNA molecules play a key role in the regulation of cellular functions, including miRNAs and long non-coding RNAs (lncRNAs). These RNA molecules regulate gene expression through a variety of molecular mechanisms, which affect cellular physiological and pathological processes. Specific RNA molecules are involved in the regulation of cell migration and invasion in EMS, as shown in Table III (31,89,107-114).

miR-93 is a miRNA that belongs to the class of non-coding RNAs. By integrating phenotypic analysis of clinical EMS samples, *in vitro* cellular experiments, and data from previous studies, miR-93 downregulation has been shown to promote aberrant proliferation, migration, and invasion of ESCs, suggesting a central role in the development and prognosis of EMS (89). A variety of miRNAs may serve as potential diagnostic markers and therapeutic targets for EMS. miR-193b-5p and miR-374b-5p show aberrant expression in the disease state and inhibited endometrial cell migration in an *in vitro* model (31).

miR-340-5p significantly reduces ESC proliferation and invasion by targeting MAP3K2 and inhibiting the MAPK/ERK signaling pathway, reducing the migratory ability, invasiveness, and EMT process of ESCs (107). However, the miR-93 regulatory mechanism identified by Lv *et al* (89) has not yet reached clinical translation. A recent study (108) demonstrated the potential of miR-30c to inhibit the invasive migration of EMS cells. miR-1229-5p shows disease severity-related upregulation of expression in ectopic ovarian endothelium, which

promotes migratory invasion and inhibits apoptosis of ESCs and Ishikawa cells by targeting STMN1 (115). Additionally, a clinicopathologic study targeting the epithelial marker E-CADHERIN and the EMT regulator miR-200b have revealed specific gene expression patterns in the *in situ* endometrium of ovarian EMS (109).

EMT is a process by which epithelial cells acquire mesenchymal properties that contribute to endometriotic cell migration and invasion. By contrast, miR-200a and miR-223-3p expression are significantly reduced in secretory phase endometriotic lesions (110). MiR-375-3p predicts disease severity by targeting NOX4, and its overexpression effectively inhibits cell proliferation, migration and invasion (111). Mechanistic studies further demonstrated that miR-182 inactivates the NF-κB pathway by directly targeting RelA, thereby inhibiting ESC proliferation, migration, invasion and the EMT process, providing a theoretical basis for the development of therapeutic strategies based on the NF-κB pathway (20). Estrogen receptor α-mediated upregulation of miR-145 promotes stromal cell migration by inhibiting the downstream target gene CITED2 (112). These findings systematically reveal the multidimensional regulatory network of miRNAs in EMS cell migration and invasion, but the precise molecular mechanisms still need to be fully analyzed.

lncRNAs are non-protein transcripts that regulate various physiological responses associated with human diseases. Their gene regulatory functions have received increasing attention, but they are still understudied in the field of EMS (116). Two landmark studies have demonstrated that DHRS4-AS1 inhibits cell proliferation and migration and induces apoptosis by regulating miR-139-5p to inhibit cell proliferation and migration and induce apoptosis (113). HOX antisense intergenic RNA regulates cell invasion and migration through the miR-519b-3p/PRRG4 axis (114). Nevertheless, the overall framework and molecular mechanisms of the role of lncRNAs in EMS remain largely unexplored.

Actins associated with cell invasion and migration. A recent review systematically summarized 13 actins and their binding proteins associated with the pathological process of EMS (115). Among these, proteins such as Talin (TLN) and Tensin (TNS) play key roles in the regulation of cell migration, adhesion and invasion (117). Talin-1 promotes the invasion, migration and adhesion of a wide range of malignant tumor cells. However, the precise functional characteristics of this receptor in the context of EMS remain to be fully elucidated. Dysregulation of Talin-1 expression results in a substantial downregulation of N-cadherin, MMP-2, and integrin β3 expression, accompanied by an increase in E-cadherin levels. Talin-1 exhibits abnormally elevated expression levels in both ectopic and ectopic endometrial tissues of patients with EMS when compared with *in situ* endometrial tissues from healthy patients. Its targeted knockdown exhibits a substantial inhibitory effect on the adherence, invasion and migration capabilities of ESCs (24). A series of studies (118-120) have revealed that TLN regulates the inflammatory microenvironment through integrin-mediated T-cell signaling cascade responses, which in turn inhibit the adhesion and migration ability of endometrial cells.

Tensin-1 (TNS1) is an actin cytoskeletal interplay protein that plays a regulatory role in various biological processes, including cell adhesion, migration, proliferation and differentiation. A clinical study (121) analyzed endometrial tissue and serum samples from patients in untreated and GnRH-a-treated groups, and found that the mRNA and protein expression levels of TNS1 in ectopic endometrial tissues were significantly reduced after GnRH-a intervention. Immunohistochemical results demonstrated that TNS1 exhibited strong positive expression in the epithelial and stromal cells of ectopic tissues in the untreated group. However, treatment significantly weakened the intensity of its expression, and the serum TNS1 concentration decreased by 53%. This finding confirms that TNS1 can be used as a dynamic marker for monitoring the response to GnRH-a treatment and highlights its potential as a molecular target for therapeutic intervention in EMS.

Invasion and migration-related integrins. EECs from patients with EMS exhibit a distinctly differentiated integrin expression profile compared with normal endometrial tissue. Integrin αvβ3 demonstrates significant overexpression in ectopic endometrial tissues, exhibiting considerably higher expression levels compared with normal endometrial tissues. This characteristic may contribute to the enhancement of adhesion, migration and invasion capabilities in ectopic cells (122). A positive correlation has also been shown between integrin expression levels and disease severity, as well as heterogeneous expression patterns in different endometrial cell subpopulations (123).

Integrin isoforms manifest distinctive expression characteristics in EMS. The co-overexpression of integrin αvβ3 and integrin β1 is pronounced in ectopic endometrial cells. Integrin αvβ3 plays a pivotal role in the adhesion, anchoring, migration, diffusion and invasion of ectopic cells by regulating the ECM signaling network (124). Conversely, elevated expression of integrin β1 is closely associated with the chronic inflammatory state of the focal microenvironment. This heightened expression has the potential to exacerbate the pathological process by enhancing cell-cell interactions and pro-inflammatory signaling (125).

At the molecular level, estrogen signaling regulates integrin expression levels through epigenetic modifications, suggesting a potential bridging role for the hormone-integrin axis in the development of EMS (126). These findings systematically elucidate the biological nature of the disease, as reflected by the heterogeneity of integrin expression. They also highlight the translational potential of integrins as novel therapeutic targets, providing innovative strategies to improve the clinical prognosis of patients through precise intervention of integrin-mediated cell-matrix interaction.

Other relevant small molecules and proteins. Small-molecule inhibitors have important regulatory functions in modulating pathological processes such as cell proliferation, migration, invasion, angiogenesis and metastasis (127). Typical examples are the FoxM1 inhibitor thiostrepton. Treatment with FoxM1 significantly reduces nasopharyngeal carcinoma cell survival and effectively blocks tumor cell proliferation, migration and invasion by inhibiting FoxM1 expression (128).

In the field of EMS research, small-molecule interventional strategies have also demonstrated therapeutic potential. Yu *et al* (129) demonstrated that the knockdown of Chemokine-Like Receptor 1 (CMKLR1) or the use of its specific antagonist, α-Naphthoyl ethyl-trimethyl-ammonium

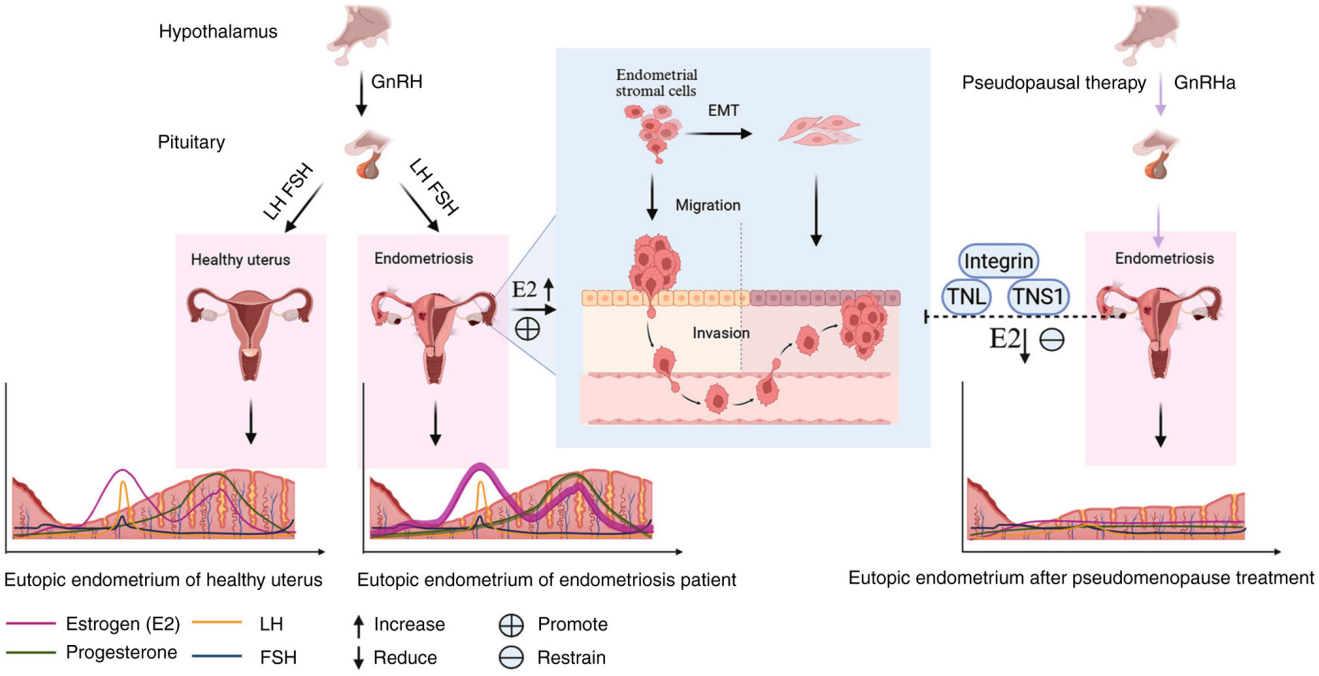


Figure 5. Relationship between endometriosis, sex hormone levels and menstrual cycle. FSH, follicle-stimulating hormone; LH, luteinizing hormone; EMT, epithelial-mesenchymal transition; GnRH, gonadotropin-releasing hormone.

iodide (α-NETA), significantly inhibited the migration and invasiveness of endometriotic stromal cells. The capacity of stromal cells to migrate and invade in patients with EMS has been demonstrated to be associated with the progression of mesenchymal-epithelial transition (MET). *In vivo* experiments have substantiated the efficacy of α-NETA in mitigating disease progression by targeting the chemokine/CMKLR1 axis. In a recent study (130), researchers examined the effects of a selective NF-κB inhibitor, namely, dihydroxy-methyl-epoxide quinimicin (DHMEQ), which was optimized using a natural compound design. This inhibitor effectively suppressed the migratory and invasive behavior of human ESCs (HESCs) at non-toxic concentrations. This observation suggests that DHMEQ could serve as a novel therapeutic agent for targeting inflammatory pathways in medical treatments.

Periostin, a member of the ECM protein family, plays a pivotal role in tissue repair, cell adhesion and signaling. Periostin stimulation significantly enhances the migratory invasion and adhesion of EMS cells through the activation of the integrin-linked kinase (ILK) 1/Akt signaling pathway (131). This suggests that it may act as an agonist in the development of EMS (132). However, the clinical translational value of periostin remains to be systematically evaluated due to the lack of *in vivo* experimental validation. Osteopontin, an integrin-binding glycoprotein, has also been shown to play a role in the adhesion and migration of ectopic foci by regulating cell-matrix interactions (25).

In addition, lipoprotein A4 (LXA4) has been shown to inhibit EMS cell migration and invasion by regulating the activity of autophagy. Li *et al* (133) found that LXA4 significantly reduced the migratory invasive ability of EMS cells by inhibiting NF-κB signaling-mediated autophagy activity. Furthermore, the reactivation of autophagy induced by rapamycin reversed this effect, thereby revealing a bidirectional regulatory role of autophagy modulation in LXA4 treatment. A previous study (60) demonstrated that the expression of T-cadherin significantly inhibited the invasive and migratory activity of ESCs. Furthermore, the expression level of T-cadherin in ectopic endometrium was significantly lower than that in the ectopic endometrium. These findings suggest that T-cadherin may be a novel therapeutic target for EMS.

Estrogen. The pathological features of EMS, a disease dependent on estrogen, are closely related to the regulation of the menstrual cycle. As demonstrated in Fig. 5, the proliferative, secretory and regressive changes of the normal endometrium are synergistically regulated by estrogen and progesterone. The two secretory peaks of estrogen (especially the secretory phase) can significantly drive the abnormal proliferation of the *in-situ* endometrium. Ectopic foci exhibit a high degree of dependence on estrogen signaling during the processes of migration, invasion and adaptation to the new microenvironment.

There is also a positive correlation between growth activity and estrogen levels. The action of estrogen is facilitated by the estrogen receptors, Erα and Erβ (134). Estrogen can significantly reduce the migratory invasive ability of cells by inhibiting ERβ expression (22). Subsequent experiments corroborated the finding that estradiol induces EMT in EECs and promotes disease progression through activation of the β-catenin/Snail signaling axis. Reverse genetics experiments have demonstrated that β-catenin knockdown completely blocks the estrogen-induced Snail-dependent EMT process (26). In addition, estrogen upregulates nicotinamide N-methyltransferase expression in ESCs in a dose-dependent manner, which regulates ESC proliferation and enhances migratory invasiveness (19).

Wakatsuki *et al* (135) determined that the estrogen receptor modulator estetrol inhibits disease progression

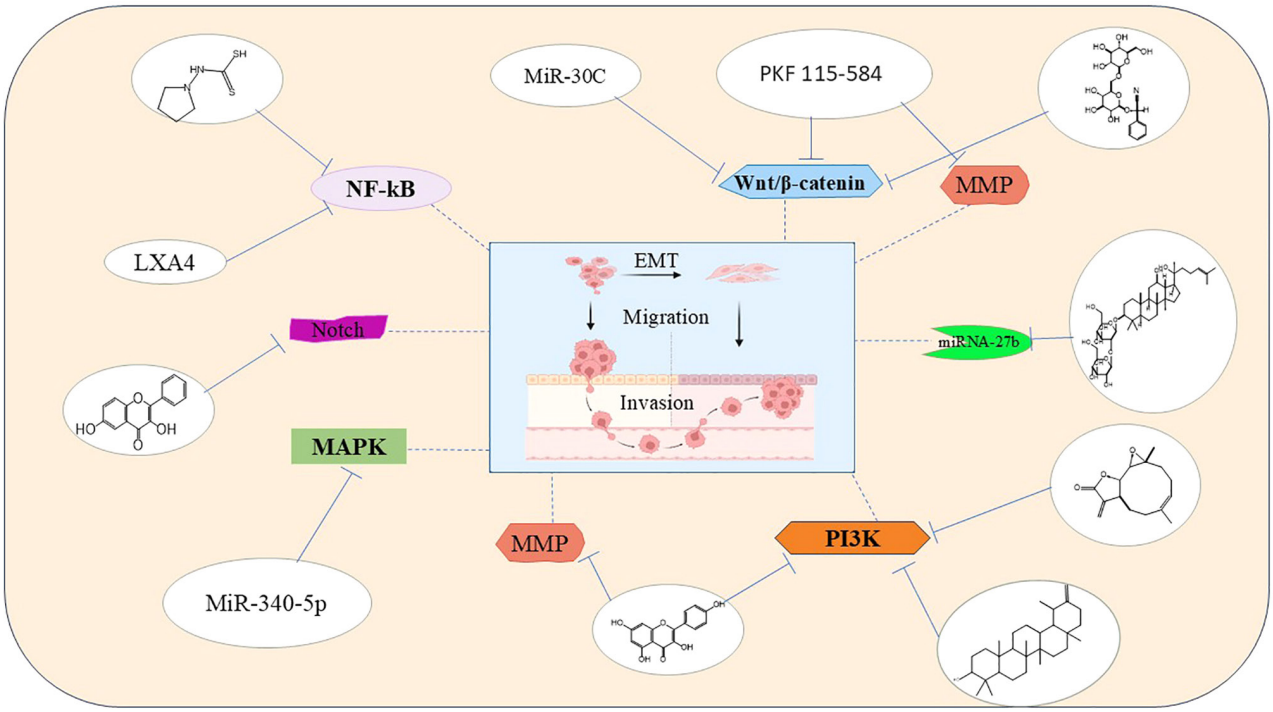


Figure 6. Inhibitors of cell migration and invasion associated with endometriosis. EMT, epithelial-mesenchymal transition; MMP, matrix metalloproteinase; miR, microRNA.

through downregulation of migration-related signaling pathways. ERβ-mediated pathological processes may engage in molecular interactions with the innate immune anti-inflammatory effects regulated by NLRC5 (136). In light of these mechanisms, contemporary therapeutic strategies are oriented toward the systematic reduction of circulating estrogen levels or the localized targeting thereof.

3. Drug studies on inhibitors of EMS cell migration and invasion

The current state of the field has resulted in the identification of various inhibitors of cell migration and invasion. These inhibitors can be categorized into several groups, including synthetic drugs and drug analogs, natural extracts, small-molecule complex inhibitors, Chinese medicine and targeted drugs. Among these inhibitors, synthetic drugs and drug analogs refer to the adjuvant therapeutic aspects that are widely used in clinical practice for the treatment of invasive diseases. Therefore, their safety, efficacy, side effects and pharmacological therapies have been demonstrated. However, the targets of action of this class of drugs are complex and diverse, and the mechanisms are more complex and cannot be explained comprehensively, especially in the treatment of cancer (137). As illustrated in Fig. 6, the mechanism of action of various pharmaceutical agents and their respective targets is concisely delineated.

Synthetic drugs, drug analogs and natural plant extracts. Natural plant extracts have become an important choice for the treatment of gynecological diseases due to their multicomponent properties and low side effect advantages. However, their complex chemical composition and mechanism of action have led to significant heterogeneity in clinical applications. More than 40 formulations and 20 compounds and monomers have been used for gynecological disease interventions, mainly targeting pathological aspects such as apoptosis, invasion, migration, oxidative stress and immunomodulation (138).

Synthetic compounds. Imatinib is a tyrosine kinase inhibitor that has been approved for the clinical treatment of two distinct conditions: chronic granulocytic leukemia and gastrointestinal mesenchymal stromal tumor. This pharmaceutical agent exhibited a substantial inhibitory effect on the proliferation of lesions and the capacity of human embryonic stem cells to invade in a three-dimensional type I collagen matrix in a mouse model of experimental EMS (139). This effect was achieved by impeding the interaction of colony-stimulating factor-1 with its receptor c-FMS. A comprehensive review of the available clinical data set (140) confirmed the antitumor efficacy of Imatinib, and *in vitro* experimentation validated the inhibitory effect on cell migration and invasion.

Pyrrolidine dithiocarbamate (PDTC) functions as a sulfhydryl-modified NF-κB inhibitor, exhibiting both antioxidant and anti-inflammatory properties (141,142). PDTC possesses the capability to induce apoptosis and to significantly inhibit adhesion, migration and invasive activity of endometriotic cells through a multi-targeted modulation process (143). This finding serves to underscore the therapeutic potential of PDTC.

β-Sitosterol, a tetracyclic triterpenoid phytosterol, is found in a variety of vegetable oils, nuts and medicinal plants (144,145). This compound exerts anticancer effects by inhibiting the proliferation and migration of malignant cells, inducing apoptosis, and interfering with metabolic pathways. A recent study expanded the application of this technique and confirmed its effectiveness in inhibiting the migration and proliferation of endometrial cells (146).

Kaempferol, a flavonoid, has garnered attention for its antioxidant, anti-inflammatory and anticancer properties (147-149). Network pharmacological predictions and *in vitro* validation suggest that the anti-EMS mechanism may involve the regulation of the PI3K pathway (150). This pathway inhibits cell migration and invasion by affecting the expression of phosphatase and tensin homolog (PTEN) and MMP-9.

Chamomile lactone, a sesquiterpene lactone, has been utilized in a variety of *in vivo* and *ex vivo* experiments, and studies have demonstrated its favorable anti-inflammatory, analgesic and anticancer properties (151-155). In addition to its inhibitory effect on the proliferation and migration of CC cells (156), a recent study confirmed its ability to reverse the EMT process in immortalized epithelial endometriotic cell line 12Z and to inhibit the invasive migratory properties of endometrial tissue implants (157).

Metformin, a well-established hypoglycemic agent, has recently emerged as a potential regulator of reproductive function and a treatment for EMS (158,159). Metformin enhances fertility by improving endometrial tolerance; however, its clinical use must be critically evaluated due to its glucose-lowering properties, which may trigger the risk of hypoglycemia in patients with normal glucose levels.

Plant extracts. Emodin (1,3,8-trihydroxy-6-methylanthraquinone), a hydroxyanthraquinone natural product, is widely found in a variety of medicinal plants (160). Emodin possesses immunosuppressive, antibacterial, anti-inflammatory and antitumor activities (161,162). However, its application in the treatment of EMS has not been fully exploited due to its physicochemical properties, such as low polarity and bioavailability.

A previous study demonstrated that rhodopsin can inhibit the migration and invasion of HESCs by targeting ILK to induce MET (163). Rhodopsin also exhibits significant antineoplastic properties, particularly against cancerous cells, while demonstrating minimal toxicity toward normal cells (164). Consequently, rhodopsin is currently regarded as a promising pharmaceutical agent with the potential to impede cell migration and invasion. Nevertheless, further refinement is necessary for its application in a clinical setting, including the optimal dosage, the ideal timing of administration, and the precise target of action.

Ginsenoside Rg3, a tetracyclic triterpenoid active ingredient of ginseng, possesses a variety of pharmacological properties, including antitumor, immunomodulatory and antiangiogenic properties (165-167). The multifunctional liposomes of Rg3 developed by Zhu *et al* (168) significantly enhanced the inhibition rate of paclitaxel-resistant cancer cells, providing an innovative direction in the treatment of drug-resistant tumors. In the context of EMS research, the administration of Rg3 has been observed to markedly diminish the fibrosis and migration potential of HESCs, a phenomenon that may be associated with the regulation of microRNA-27b-3p (169). However, despite the significant antitumor effects of ginsenoside Rg3, its clinical application is still subject to some limitations. For instance, the specific molecular targets of this agent have not been thoroughly investigated, which may impede its widespread clinical application.

Berberine (BBR), a quaternary alkaloid, is found in a variety of medicinal plants, including *Rhizoma Coptidis*, and has been shown to possess anti-inflammatory, anticancer and metabolic regulatory properties (170-175). BBR exerts its inhibitory effects on the proliferation, invasion and migration phenotypes of HESCs by decreasing the expression of miRNA-429. However, the overexpression of miR-429 has been shown to reverse these effects (176,177).

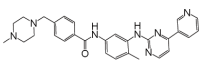
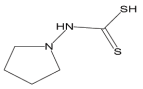
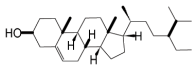
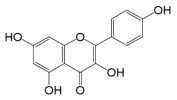
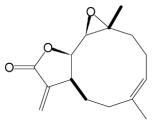
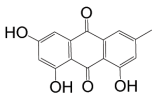
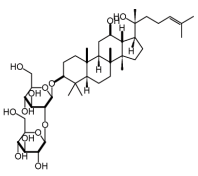
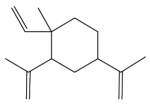
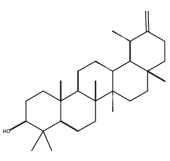
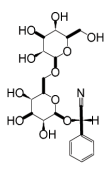
In vitro studies have demonstrated that β-elemene, a constituent of turmeric extract, exhibits significant inhibitory effects on the proliferation and migration of endometriotic cells (178). Taraxerol has also been shown to induce apoptosis and to inhibit ectopic cell proliferation and migration by blocking the PI3K/Akt/mTOR signaling pathway (179). Conversely, amygdalin has been shown to impede HESC proliferation, migration and invasion by modulating the Wnt/β-catenin signaling axis (35). These natural extracts are predominantly in the experimental research stage, and their clinical translation necessitates substantial sample data and systematic pharmacodynamic validation, as evidenced in Table IV (35,139,143,146,150,157,163,169,178,179).

Molecular inhibitors and melatonin. The role of interleukin-1β (IL-1β) in EMS is primarily characterized by its promotion of EESC proliferation, migration and invasion. IL-1β may act as a positive regulator affecting the progression of EMS, acting through multiple mechanisms. For instance, a group study (180) found that LXA4, as revealed by *in vitro* experiments, may inhibit the progression of EMS cell migration and invasion in part by decreasing or increasing the action of IL-1β. A previous study reported the use of a small-molecule antagonist of the Tcf/β-catenin complex, which inhibited MMP-9 activity in endometriotic epithelial and stromal cells, thereby suppressing cell proliferation, migration and invasion (181). Additionally, a robust correlation has been observed between cell migration and invasion and MMP-9. Consequently, a small-molecule antagonist of the Tcf/β-catenin complex may impede migration and invasion by hindering the Wnt/β-catenin pathway. However, the potential utilization of this approach in the management of EMS remains to be elucidated through further investigation.

Fibrinogen α-chain (FGA) plays a role in EMS and is a cell adhesion molecule containing two arginine-glycyl-aspartate (RGD) sequences that bind to integrins. A strong correlation between elevated levels of FGA and tumor progression and metastasis has been demonstrated. For instance, FGA has been identified as a promising biomarker for BC (182). Furthermore, the migration and invasion of the endometrial stromal cell line hEM15A can be substantially hindered by the inhibition of FGA (183). A team of researchers conducted a study to analyze the effect of FGA on the biological behavior of EuESCs (184). The findings indicated that the knockdown of FGA led to a suppression in the migratory and invasive capabilities of EuESCs. Additionally, the study revealed alterations in the distribution and morphology of the cytoskeletal filaments, which represents a novel observation that suggests the potential for FGA inhibitors to be utilized as therapeutic agents for the treatment of EMS.

Melatonin, an amine hormone secreted by the pineal gland of the brain, is chemically known as N-acetyl-5-methoxytryptamine and belongs to the indole heterocyclic class of compounds, which is a small-molecule neuroendocrine hormone. Melatonin has an inhibitory effect

Table IV. Inhibitors of chemically synthesized and naturally derived compounds associated with endometriosis cell migration and invasion.

First author/s, year	Name	Structure	Mode of action	Limitations	(Refs.)
Griffith *et al*, 2010	Imatinib		Decreases migration	No clinical trials of degradation have been conducted yet.	(139)
Zhang *et al*, 2011	Pyrrolidine dithiocarbamate		Inhibits NF-κB activity	No clinical trials of degradation have been conducted yet.	(143)
Wen *et al*, 2023	β-Sitosterol		Inhibits TGF-β-induced phosphorylation	Mechanism needs production further study.	(146)
Zhao, *et al*, 2022	Kaempferol		Inhibits PI3K	Lack of *in vivo* experimental validation.	(150)
Kabil *et al*, 2023	Parthenolide		Inhibits PI3K/AKT/GSK-3β/nβ-catenin	Mechanism needs further study.	(157)
Zheng *et al*, 2016	Emodin		Inhibits migration and invasion abilities by facilitating the epithelial-mesenchymal transition through targeting ILK	Lack of *in vivo* experimental validation.	(163)
Kim *et al*, 2017	Ginsenoside Rg3		Decreases fibrotic and invasive by modulating miRNA-27b	No clinical trials have been conducted yet.	(169)
Fu *et al*, 2025	β-ELE		β-ELE inhibits the proliferation and migration of endometriotic cells *in vitro*	No clinical trials	(178)
Liu *et al*, 2025	Taraxasterol		Inhibits the proliferation and migration of endometrial ectopic cells and promotes apoptosis through the PI3K/Akt/mTOR pathway.	Lack of *in vivo* experimental validation	(179)
Yu *et al*, 2024	Amygdalin		Inhibits endometrial stromal cell proliferation, migration and invasion in endometriosis mice via inhibiting Wnt/β-catenin signaling	No clinical trials of degradation have yet been conducted	(35)

on tumor cells and complements conventional cancer treatment modalities. Melatonin also significantly reduces tumor load in OC by inhibiting the invasion and migration of OC stem cells (185-187). In addition, in 2018, Qi *et al* (188) discovered that melatonin could impede the migration, invasion and EMT of normal and endometriotic EECs. Previous studies have identified the potential anticancer activity of melatonin, as well as its ability to inhibit tumor cell growth (189), invasiveness (190) and angiogenesis (191). This finding warrants further investigation through internal and external experiments to verify its

clinical relevance. The exploration of the anticancer properties of melatonin represents a novel and promising research direction that merits continued attention (192).

Traditional Chinese medicines (TCMs). With the advent of molecular biology and network pharmacology, the therapeutic strategies of TCM for EMS have been the subject of new insights and advances. Juan-tong-yin induces endoplasmic reticulum stress through activation of the unfolded protein response, which has been demonstrated to significantly enhance the level of autophagy in ESCs (34). This process has been linked not only to endoplasmic reticulum stress-mediated apoptotic mechanisms, but also to the effective promotion of programmed endometrial cell death in patients with EMS. Furthermore, it has been observed to significantly inhibit the migratory invasive ability of ESCs. Autophagy, a core mechanism of cellular homeostasis regulation, has the potential to remodel the intracellular environment through the Juan-Tong-Yin-mediated lysosomal degradation pathway. This may intervene in the pathological process of EMs.

The c-Jun N-terminal kinase (JNK) signaling pathway is a key signaling pathway in the stress response, whose activation promotes apoptosis. In the context of stress signaling regulation, the Jiangpingni formula has been demonstrated to induce ectopic ESC apoptosis and inhibit their abnormal proliferation by specifically activating the JNK signaling pathway. This provides a novel paradigm for therapies targeting the cell death pathway (193).

Conversely, the Yushén Huǒyào Formula has been shown through multi-omics analysis to modulate the tumor necrosis factor (TNF) signaling pathway, thereby significantly improving the inflammatory microenvironment of EMS lesions (194). A study found that Luoshi Neiyi prescription is capable of inhibiting the adhesion, migration and invasion of ESCs (71). This effect was significantly superior to that of danazol. This conclusion was reached through the implementation of network and serum pharmacology combined with *in vitro* and *ex vivo* experiments. A recent study also revealed that Hua Yu Xiao Zheng Decoction exerts antioxidant and anti-aging effects by inhibiting the PI3K/Akt signaling pathway (195). Concurrently, it effectively blocks the proliferation and migration activity of ectopic ESCs

Chinese herbs such as Juan-Tong-Yin, Jiang Ping Ni formula and Yu Shen Huo Yao formula affect the proliferation, migration and invasion of endometriotic cells through different mechanisms, including enhancement of autophagy, activation of JNK signaling pathway to induce apoptosis, as well as modulation of TNF signaling pathway and inhibition of hypoxia-inducible factors. The studies thereof suggest novel approaches and strategies for the treatment of EMS and demonstrate the therapeutic potential of TCM.

Relevant therapeutic targets. To improve the prognosis for early screening and diagnosis of EMS, the discovery of more specific predictive targets is essential. A number of specific targets have been identified through analysis of clinical samples or validation through *in vivo* and *in vitro* experiments. Significant gene expression changes and cytokine alterations present in the endometrium of patients with EMS, which may enhance the formation of EMS lesions and provide new therapeutic targets, are shown in Table V (33,136,196-203). Drugs aimed at these targets may have therapeutic benefits, but further clinical validation is needed.

4. Clinical applications

There are few clinical applications for drugs that inhibit EMS cell migration and invasion. Currently, the most commonly used drugs are hormonal therapies, including oral contraceptives (estrogen-progestin preparations), progestin preparations (containing progestin derivatives), androgens (danazol) and GnRH agonists and antagonists (204). Oral contraceptives are still not as effective as expected in improving pain (205). Progestogens, although cheaper than other drugs, have side effects such as progressive uterine bleeding, weight gain, breast discomfort, headache, nausea and mood changes (206). Furthermore, progesterone derivatives usually have longer treatment cycles (207).

Danazol, a derivative of the hormone testosterone, is also used to treat EMS by reducing pituitary secretion of follicle-stimulating hormone and luteinizing hormone by inhibiting GnRH secretion, but there are adverse effects and poor compliance (207,208). Pseudopausal therapy drugs include GnRH-a and danazol, which lower the estrogen levels in patients with EMS. These elicit temporary menopause, so that the ectopic endothelium atrophies and achieves the therapeutic purpose (Fig. 6). Therapy can be achieved by regulating TNS, TNL and integrins to inhibit EMS cell migration and invasion (24,121,209). TNS, TNL and integrins are the main molecules affecting the migration and invasion of EMS cells. Pseudopausal therapy not only controls the disease progression from the level of lowering estrogens but also inhibits the proliferation from the cellular molecular level.

Compounds, natural extracts, molecular inhibitors, TCM and related targets can inhibit migration and invasion in EMS cells, although most studies are in the experimental research phase. Anexelekto (Axl), a member of the receptor tyrosine kinase family Tyro3, Axl and Mertk. Axl is phosphorylated and activated by binding to its natural ligand, with growth arrest activated by phosphorylation through binding to its natural ligand, growth-stopping-specific protein 6 (Gas6). Axl plays an important role in tumor cell growth, migration, invasion and immunosuppression (210-212). Small-molecule tyrosine kinase inhibitors and monoclonal antibodies (mAb) are the main Axl inhibitors, and there have been numerous clinical trials for use thereof in patients with cancer (213). This has not yet been applied to the treatment of EMS. However, the rational and effective use of these antibodies is expected to enhance the therapeutic effect (214).

The study of pathogenesis of EMS and related inhibitors remains a complex area of research. Certain agents that have been used to inhibit cell migration and invasion in other tumors, including flavonoids (215), curcumin (216), rhodopsin (164) and ginsenosides (169), must be tested for toxicologic and pharmacokinetic properties before they can be formally applied in the clinic. Thus, one of the major obstacles to research to translate preclinical findings into clinical practice is the lack

Table V. Targets associated with endometriosis cell migration and invasion.

First author/s, year	Target	Definition	Study methodology	Impact	Limitations	Role	(Refs.)
Miller *et al*, 2013	ADAMs	The principal enzymes for shedding RTK ectodomains	*In vitro* cell experimental proteomics	Reduces cell migration	Small sample size and lack of long-term prognosis studies	Future use as therapeutic target	(196)
Shi *et al*, 2024	KLF6	A transcription factor	*In vitro* two-cell experiment validation t	Inhibits the proliferation, migration and angiogenesis	Lack of *in vivo* experimental validation	Targeted therapy for EMS	(33)
Zanon *et al*, 2024	Ang II	Cardiovascular active peptide	*In vivo* and *in vitro* experimental validation	Regulates hESC proliferation and migration through tPA-uPA/uPAR pathway activation	Small clinical samples	Treatment	(197)
Chen *et al*, 2023	AGPAT4	Integral to the AGPAT family	Multi-omics study of clinical tissue samples	The siRNA-mediated silencing of AGPAT4 resulted in a marked inhibition of interstitial cell proliferation, migration and invasion	No further molecular interactions and functional roles for AGPAT4	Potential for biomarkers and therapeutic targets	(198)
Zheng *et al*, 2023	HIF1AN	Hypoxia-inducible factor 1 subunit alpha inhibitor	*In vivo* and *in vitro* experimental validation	miR-429 targets HIF1AN in HESCs	Investigations are needed to clarify the role of the miR-429/HIF1AN axis in EM in the future	Treatment	(199)
Zhang *et al*, 2025	FZD7	Transmembrane receptor protein	Endometrial stromal cells (ESCs) and human ectopic endometrial stromal cell line hEM15A	Regulates endometriotic cell proliferation, invasion, migration, and angiogenesis via ferroptosis	Lack of *in vivo* experimental validation	Treatment	(200)
Lv *et al*, 2025	METTL14	RNA methyltransferase	human ESC (HEM15A)	Inhibits he activation of the MEK/ERK pathway and ESC proliferation, migration, and invasion	Various drugs and plasmids were used to treat the cells.	Treatment	(201)

Table V. Continued.

First author/s, year	Target	Definition	Study methodology	Impact	Limitations	Role	(Refs.)
Tang *et al*, 2024	RNF43	Ubiquitin ligase	Primary ectopic ESCs	Negatively affects viability and migration of ESCs	No further molecular interactions and functional roles for RNF43	Treatment	(202)
Vu *et al*, 2024	APOBEC3B	DNA editing	12Z immortalized human endometriotic cell line	Inhibits cell proliferation, invasion and migration	Lack of clinical research	Therapeutic target	(203)
Guo *et al*, 2024	NLRC5	NOD-like receptors family	Human ESCs	Inhibits migration	Small clinical samples	Treatment	(136)

ESCs, endometrial stromal cells; ADAMS, A Disintegrin and Metalloproteinases; RTK, receptor tyrosine kinase; KLF6, Krüppel-like Factor 6; Ang II, angiotensin II; FZD7, Frizzled-7; METTL14, methyltransferase-like 14; RNF43, RNF43, ring finger protein 43; APOBEC3B, Apolipoprotein-B mRNA-editing complex 3B; NLRC5, NOD-like receptors (NLRs) family CARD domain-containing 5.

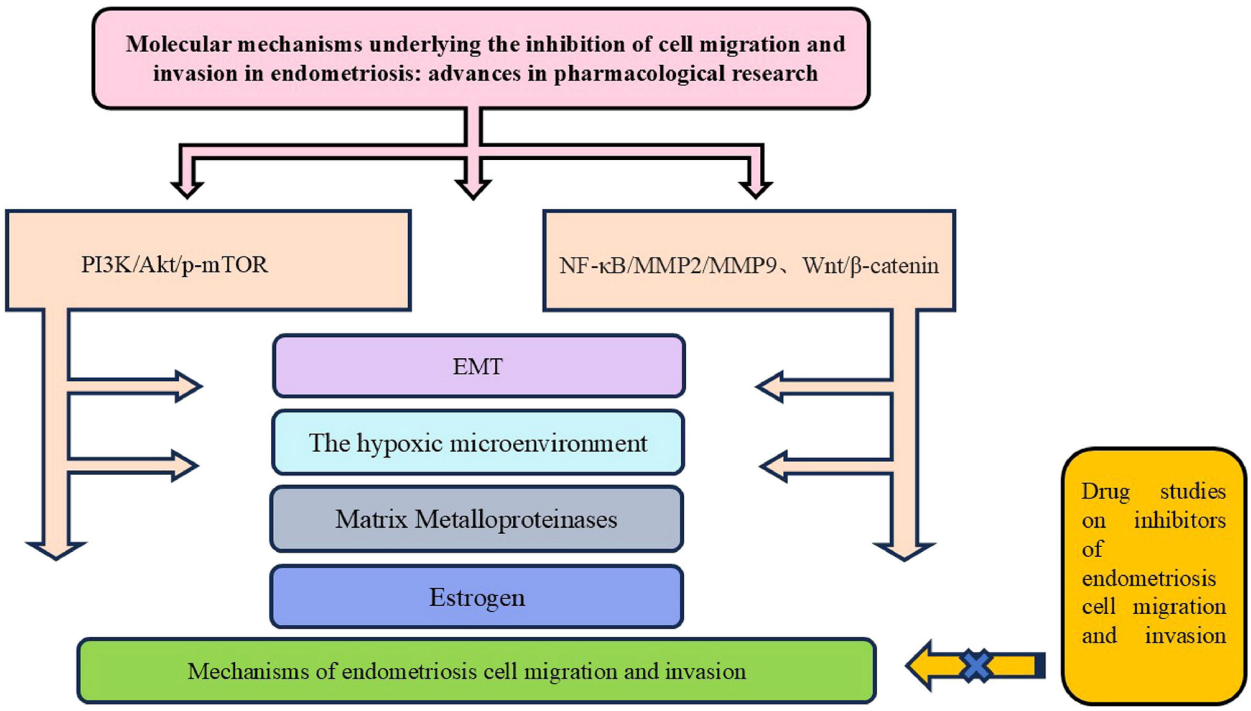


Figure 7. Full text graphic summary. EMT, epithelial-mesenchymal transition; MMP, matrix metalloproteinase.

of robust *in vivo* models to accurately summarize the complex pathophysiology of EMS.

Current animal models, such as the mouse xenograft model or the rat autograft model (217), provide valuable insights but often do not fully mimic human disease progression due to differences in immune responses and hormonal regulation. Other studies have identified endometrial-like organs (218) and xenografts between homozygous rats and mice (219). This is critical for the development of more representative *in vivo* systems to validate the efficacy and safety of potential inhibitors prior to conducting clinical trials.

Another major obstacle lies in optimizing drug delivery to effectively target endometriotic lesions. Systemic delivery of drugs may result in off-target effects and inadequate site-of-action concentrations, especially given the unique

microenvironment of endometriotic lesions, for example, hypoxia and ECM remodeling (68,72). Novel delivery systems, for example, a cRGD-modified liposome nanodrug (cRGD-LP-ART), have been synthesized, offering promising solutions by improving drug stability, bioavailability and specificity (220). Similarly, topical administration via intrauterine devices can circumvent systemic exposure and improve outcomes in patients with deep invasive EMS (221).

5. Summary

EMS is a common benign gynecologic disease, but the invasive and metastatic nature thereof leads to complex and limited treatment. Cell migration and invasion are important pathological processes in EMS, involving complex signaling pathways and multiple influencing factors, which not only increase the complexity of targeted therapies, but also increase the difficulty of treatment. In the past, a solution has not been found, and there are still some challenges and limitations. There is also no completely eradicable clinical treatment at present.

According to the present review (Fig. 7), numerous researchers have found that cell migration and invasion can be inhibited by regulating small molecules and other mechanisms that involve the activation and regulation of signaling pathways. Although these treatments have shown some efficacy, they may have adverse effects in terms of reproductive function and embryotoxicity. Therefore, a comprehensive understanding of the signaling networks associated with EMS cell migration and invasion, the integration of multiple pathways and targets, and the development of new plant extracts to inhibit lesions are all therapeutic approaches that will provide new directions for future research.

In conclusion, the rational use of drugs targeting the migration and invasion of endometriotic cells is expected to address the problems of misdiagnosis, delayed diagnosis and reduced fertility in patients with EMS. Follow-up studies need to focus on the following three issues. First, to establish a dynamic balance of efficacy-toxicity evaluation systems and clarify the quantitative relationship between the dose threshold and the threshold of adverse effects in the therapeutic window. Second, to construct a female physiological simulation model integrating neuroendocrine cycle regulation, emotional stress responses, and the gastrointestinal metabolism microenvironment. This model must focus on the dynamic expression of estrogen receptors, the feedback mechanism of the hypothalamus-pituitary axis, the interaction between the 5-HTergic system and hypothalamic-pituitary-adrenal axis, the kinetics of substance transport in intestinal and hepatic axes, and the metabolism of bacterial flora and other key elements. Third, the development of targeted intervention strategies, including specific modulation of signaling pathways based on single-cell multi-omics resolution or the combination of multiple therapeutic approaches to improve therapeutic efficacy. In addition, future research should prioritize improving *in vivo* models, exploring innovative drug delivery platforms, and fostering interdisciplinary collaborations to accelerate the transition from bench to bedside. By addressing these translational challenges, the relevance of the findings to real-world treatment strategies will be strengthened.

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Authors' contributions

NW, RZ and ZD designed and wrote the review. HG, YZ, JS, JM, RS and XQ revised and provided comments during all stages of writing the manuscript. All authors contributed for the final version of the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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