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Mini-Review

Developments in reproductive biology and medicine

Overview of crosstalk between stromal and epithelial cells in the pathogenesis of adenomyosis and shared features with deep endometriotic nodules

Margherita Zipponi [1], Luciana Cacciottola [1], and Marie-Madeleine Dolmans [1,2,*]

[1]Pôle de Gynécologie, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, Belgium
[2]Gynecology Department, Cliniques Universitaires St-Luc, Brussels, Belgium

*Correspondence address. Pôle de Gynécologie, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Avenue Mounier 52, bte B1.52.02, 1200 Brussels, Belgium. Tel: +32-2-764-5287; E-mail: marie-madeleine.dolmans@uclouvain.be https://orcid.org/0000-0002-6331-3026

ABSTRACT

Since the first description of adenomyosis more than 150 years ago, multiple hypotheses have attempted to explain its pathogenesis. Indeed, research over recent years has greatly enhanced our knowledge of the underlying causes. This has opened up avenues for the development of strategies for both disease prevention and treatment of its main symptoms, such as pelvic pain, heavy menstrual bleeding, and infertility. However, the current means are still largely ineffective, so it is vital that we shed light on the pathways involved. Dysregulated mechanisms and aberrant protein expression have been identified as contributing factors in interactions between endometrial epithelial and stromal cells, ultimately leading to the growth of adenomyotic lesions. These include collective cell migration, epithelial-to-mesenchymal transition, hormonal influence, and signaling from non-coding RNAs and extracellular vesicles. We provide a concise summary of the latest insights into the crosstalk between glands and stroma in ectopic adenomyotic lesion formation. While there is an abundance of literature on similarities between adenomyosis and deep endometriosis, there are insufficient data on the cytochemical, molecular, and pathogenetic mechanisms of these two disorders. However, various shared features, including alterations of cell adhesion molecules, abnormal hormone regulation, and the presence of cancer-driving mutations and epigenetic modifications, have been identified. Nevertheless, the pathogenic mechanisms that contribute to the cause and development of these enigmatic diseases have not been fully elucidated yet.

Keywords: adenomyosis / endometrium / endometrial cells / collective cell migration / epithelial-to-mesenchymal transition / microRNAs / extracellular vesicles / deep endometriotic nodules

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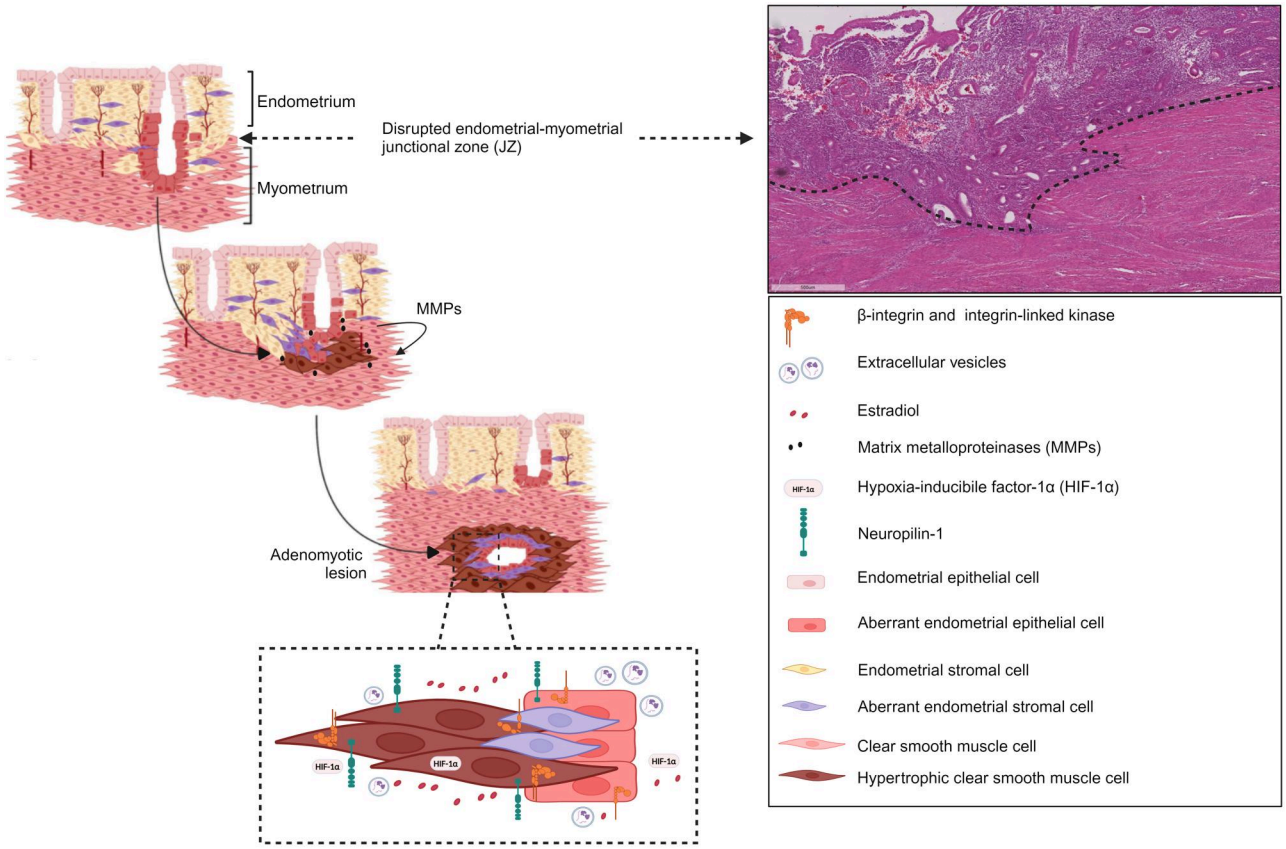
GRAPHICAL ABSTRACT



Factors involved in the crosstalk between glands and stroma in the development of ectopic adenomyotic lesions.

Introduction

Adenomyosis is a common and chronic estrogen-driven condition (Devlieger *et al.*, 2003; Vannuccini and Petraglia, 2019; Chapron *et al.*, 2020). Its prevalence in the general population of women of reproductive age ranges from 20% to 35% (Naftalin *et al.*, 2012; Pinzauti *et al.*, 2015). Higher rates have been observed among patients with endometriosis and concurrent infertility (35–79%), or with endometriosis and symptoms of heavy and/or painful menses (38–87%) (Upson and Missmer, 2020). Adenomyosis is a heterogeneous disease characterized by the presence of ectopic endometrial glands within the myometrium. It manifests mainly in two different forms: (i) diffuse adenomyosis when numerous foci of endometrial glands and stroma are dispersed throughout the myometrium; and (ii) focal adenomyosis when the disease forms clusters in a single nodule (Bergeron *et al.*, 2006; Chapron *et al.*, 2017). The insidious clinical presentation and common association with endometriosis make the diagnosis of adenomyosis quite challenging (Leyendecker *et al.*, 2015; Chapron *et al.*, 2017; Donnez *et al.*, 2019). Symptoms of uterine adenomyosis like pelvic pain (dysmenorrhea, dyspareunia, and chronic pelvic pain), heavy menstrual bleeding (HMB), and/or infertility could present years later, as this disease may be asymptomatic in up to one-third of cases (Vannuccini and Petraglia, 2019; Sarıdoğan and Topbas Selcuki, 2022). Late diagnosis, which until very recently relied on confirmation by histological examination following hysterectomy, further complicates investigations into this disease using *ex vivo* tissue samples. Indeed, histological features of adenomyosis in some uteri may show a later and more severe disease stage, not representative of all clinical situations. Today, imaging techniques help clinicians to better scrutinize the uterine architecture, with magnetic resonance imaging (MRI) and transvaginal ultrasound serving as increasingly accurate and non-invasive diagnostic tools for adenomyosis (Bazot and Daraï, 2018; Exacoustos *et al.*, 2022; Alcázar *et al.*, 2023).

Despite being a major issue in young women's health and quality of life, the etiology and pathogenesis of adenomyosis have not yet been elucidated, but three main theories dominate the literature: (i) invasion of the myometrium by endometrial tissue via a traumatized endometrial-myometrial junction resulting from micro-traumatization of the endometrial-myometrial interface, with activation of the tissue injury and repair mechanism (Leyendecker *et al.*, 2009); (ii) metaplasia of displaced embryonic pluripotent Müllerian remnants; and (iii) differentiation of adult stem cells (García-Solares *et al.*, 2018a; Zhai *et al.*, 2020; Cheng *et al.*, 2023). In any case, these cells can turn into ectopic endometrial tissues in the myometrial wall and trigger adenomyotic lesions by differentiating into endometrial stroma and glands (Vannuccini *et al.*, 2017; Donnez *et al.*, 2021). Increasing evidence in the literature indicates that eutopic endometrium may undergo molecular changes conducive to development of specific characteristics, favoring a phenotype that involves increased proliferation, migration and invasion of endometrial cells, collective cell migration (CCM), epithelial-to-mesenchymal transition (EMT), enhanced angiogenesis, reduced apoptosis, impaired immune function, dysregulated extracellular matrix (ECM) function, and altered hormone levels (increased estrogen production

and progesterone resistance) (Yang *et al.*, 2007; Stratopoulou *et al.*, 2021a). Shedding light on the mechanisms underlying the pathogenesis of this enigmatic disorder will help us develop targeted therapies to treat the disease since, so far, there are only symptomatic therapies acting on pain and HMB. These treatments show limited effectiveness in terms of treating uterine infertility, and there is no medical therapy able to prevent or cure lesions at present (Vannuccini and Petraglia, 2019; Stratopoulou *et al.*, 2021a).

Identification and histological characterization of ectopic lesions in adenomyosis

Adenomyosis is histologically characterized by irregularly shaped islands of endometrium-like glands and stroma within the myometrium. A positive histopathological diagnosis is made in the presence of epithelial glands and stroma at a distance of 2.5 mm beneath the endometrial-myometrial junction (the most widely accepted criterion) (Vercellini *et al.*, 2006; Zaloudek *et al.*, 2011), or even ≥4 mm according to other publications (Vercellini *et al.*, 1993). Clear smooth muscle hyperplasia and hypertrophy surrounding ectopic endometrial foci also constitute a strict diagnostic criterion (Bird *et al.*, 1972; García-Solares *et al.*, 2018b; Chapron *et al.*, 2020). Tissue sections of adenomyotic lesions show multiple irregularly shaped and apparently interconnected endometrial glands embedded in the stroma. In fact, its components architecturally resemble the basalis layer of eutopic endometrium, where a complex longitudinally connected glandular structure is normally formed (Antero *et al.*, 2020; Camboni and Marbaix, 2021). Some functional aspects of ectopic endometrium also differ from normal eutopic endometrium. Matsumoto *et al.* (1999) found that Ki67 expression in endometrial epithelial cells (EECs) of adenomyotic lesions was constantly upregulated, irrespective of the menstrual phase. A study by Li *et al.* (2019 points to upregulation of Bcl-2, an anti-apoptotic protein, in endometriotic lesions during both proliferative and secretory phases, possibly due to raised levels of estrogen receptor (ER) expression in endometrial stromal cells (ESCs) of women with adenomyosis. As a result, cells become less sensitive to apoptosis, allowing them to evade it, while supporting constant proliferative activity, migration to, and implantation in ectopic lesions (Matsumoto *et al.*, 1999; Li *et al.*, 2019). By investigating caspase 3-induced apoptosis and autophagosome ($LC3b^{+}$)-induced autophagy, mechanisms involved in cell death and survival, d'Argent and colleagues demonstrated substantial differences between adenomyotic lesions and eutopic endometrial tissue in subjects with and without the disease. Indeed, apoptosis and autophagy were decreased in adenomyotic lesions compared to native endometrium, suggesting that aberrant cell survival may be involved in lesion development (d'Argent *et al.*, 2023). The hypothesis suggesting that adenomyotic lesions may be present from birth is supported by the ability of cells to circumvent apoptosis, indicating their potential longevity and persistence. Next-generation sequencing on a comprehensive panel of adenomyotic and endometriotic tissues recently revealed the presence of cancer-driving mutations affecting KRAS in endometrial EECs (Bulun *et al.*, 2023). Some mutations detected in adenomyotic lesions were also found in adjacent eutopic endometrium, implying that they most likely arose in eutopic EECs before they invaded the myometrium (Inoue *et al.*, 2019). All in all, these findings indicate that KRAS-mutated clones originating in eutopic endometrium acquire greater invasive and survival capacities that facilitate adenomyosis establishment. On the other hand, ESCs from women with adenomyosis display many epigenetic abnormalities in DNA methylation, histone modification, and micro(mi)RNA expression, giving rise to abnormal mRNA and protein expression, including that of ERs and progesterone receptors (PRs) (Bulun *et al.*, 2021).

Evidence of interactions between stromal and epithelial components in ectopic adenomyotic lesion development

Collective cell migration

The concept of CCM originates from a study conducted in 2013 in a baboon model of deep endometriotic nodules (Donnez *et al.*, 2013). Donnez *et al.* found that one year after inducing the disease, there was no significant difference in levels of cell–cell adhesion markers E-cadherin and β-catenin between the most and least aggressive endometriotic glands (Orellana *et al.*, 2017). CCM is characterized by preservation of cell–cell attachments during any large-scale, coordinated migration of groups of cells, which can happen in both physiological and pathological contexts (Friedl and Alexander, 2012). In case of deep endometriotic nodules, CCM has been implicated in lesion invasiveness (Donnez *et al.*, 2015; García-Solares *et al.*, 2018b), which is why Donnez *et al.* (2015) suggested that this process might also be involved in invasiveness in adenomyosis. During CCM, cells within the migrating group remain physically and functionally connected, and their migration is facilitated by multicellular polarity and organization of the actin cytoskeleton, generating a force for cell traction and protrusion. As these cell groups migrate, they may cause structural modifications to surrounding tissue, either by creating a clear pathway or modifying the ECM (Fig. 1). A recent transcriptomic study by Zhai *et al.* (2022) endorses the significant role that CCM may play in ectopic endometriotic lesion formation. Chemokines within the anatomical niche like CXCL/CXCLR and growth factors are crucial to establishing and maintaining collective cell polarity and migration, vital to CCM. In the context of adenomyosis, Stratopoulou *et al.* (2023) recently provided evidence that upon M2 macrophage exposure, endometrial cells from women with adenomyosis acquire a more invasive phenotype than their healthy counterparts. This suggests that macrophages alone may be sufficient to promote the disease. Furthermore, EECs from adenomyosis patients become significantly more invasive when interacting with macrophages than EECs from healthy subjects. Hence, these cells may be more susceptible to the action of local macrophages, becoming the determining factor for disease development in adenomyosis patients (Stratopoulou *et al.*, 2023). Further research in this area will provide a better understanding of the mechanisms involved and the contribution of CCM to the pathogenesis of the disease.

Role of matrix metalloproteinases

A less dense ECM can potentially facilitate endometrial cell migration and invasion of the myometrium, participating in adenomyosis development. Matrix metalloproteinases (MMPs) are enzymes known to be implicated in tissue degradation, particularly during menstruation (Marbaix *et al.*, 1996; Salamonsen and Woolley, 1996), as shown in Fig. 2. Several studies have reported increased stromal MMP expression, particularly that of MMP-2 and MMP-9, in eutopic endometrium from adenomyosis patients compared to healthy endometrium (Wang and Chen, 2022; Zhai *et al.*, 2022; d'Argent *et al.*, 2023; Stratopoulou *et al.*, 2023). Li *et al.* also demonstrated a positive correlation between MMP expression and vascular endothelial growth factor (VEGF), suggesting

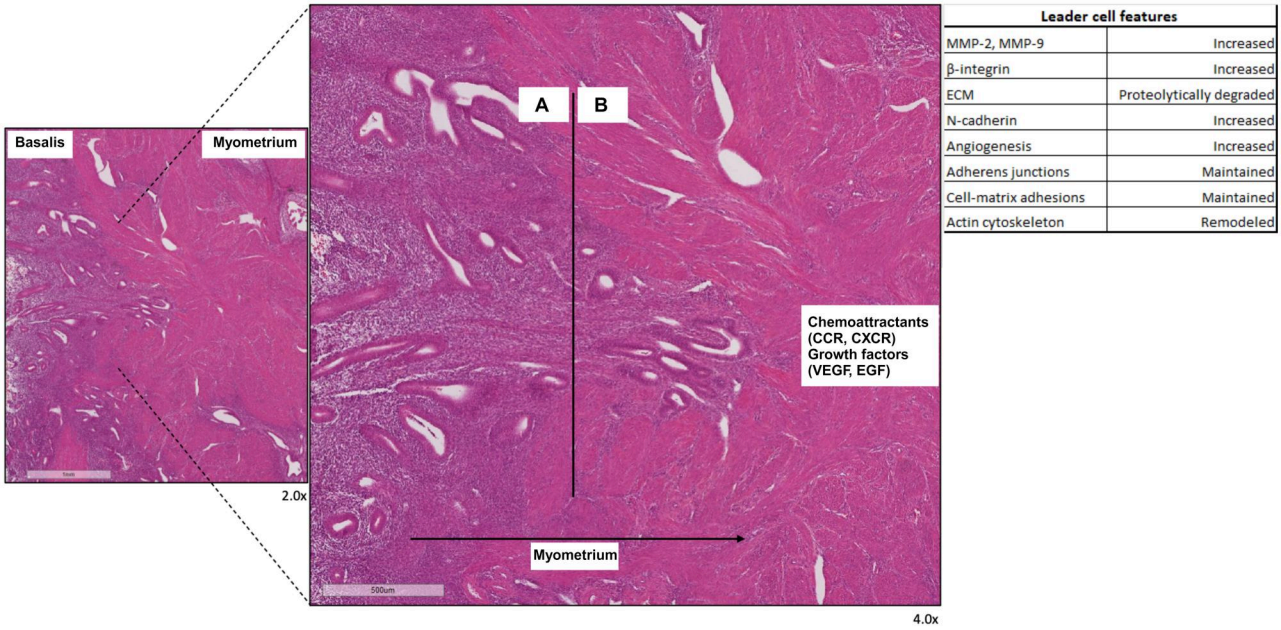


Figure 1. Collective cell migration, a proposed mode of cell movement driving adenomyosis development: histological appearance of the initiation of adenomyosis. (**A**) Follower glands and stroma. (**B**) Leader glands and stroma. ECM, extracellular matrix; MMPs, matrix metalloproteinases; VEGF, vascular endothelial growth factor; EGF, epithelial growth factor; CCR/CXCR, chemokine receptor.

increased angiogenesis. This enhanced angiogenesis may further promote invagination of the endometrium into the myometrium, thereby contributing to disease development (Li *et al.*, 2006). In brief, overexpression of MMP-2 and MMP-9, along with enhanced angiogenesis, point to their involvement in the invasive behavior of endometrial cells and development of adenomyosis. These findings shed light on the potential role of ECM remodeling and angiogenesis in the pathogenesis of the disease.

Epithelial-to-mesenchymal transition

Another biological mechanism potentially implicated in adenomyosis development and progression may be EMT. This process is characterized by disruption of cell–cell junctions, loss of apicobasal polarity, and transition from epithelial gene expression to mesenchymal gene expression (Chen *et al.*, 2010; Friedl and Alexander, 2012). EMT culminates in cells acquiring mesenchymal properties, including greater motility and invasiveness. The occurrence of these mechanisms in adenomyosis was first reported in a 2010 study, when researchers observed downregulation of E-cadherin, but upregulation of vimentin and N-cadherin, in EECs from adenomyotic lesions (Chen *et al.*, 2010; Zhou *et al.*, 2018). Various studies have provided evidence of adhesion molecules being associated with EMT in adenomyosis (Fig. 2). Upregulation of Talin1, an intracellular cytoskeletal protein and major component of the focal adhesion complex, and downregulation of Cav-1, a plasma protein, were reported in both eutopic and ectopic endometrial glands from women with adenomyosis. This points to their potential involvement in the development of adenomyotic lesions by EMT and also activation of the β-catenin pathway (Zhao *et al.*, 2013; Jiang *et al.*, 2016; Wang *et al.*, 2021a). A number of other factors, like the miR-200 family and miR-205 miRNAs, hepatocyte growth factor (HGF), neuropilin-1 (NRP1), integrin-linked kinase (ILK), estradiol (E2), S-phase kinase-associated protein 2 (SKP2), and platelets, have also been put forward as potential regulators of EMT in adenomyosis (Fig. 2). However, these factors remain contentious and subject to debate. For example, platelets were previously detected in adenomyotic lesions, but not in healthy endometrium, suggesting their possible role in the EMT process and subsequent fibrogenesis (Liu *et al.*, 2016). However, a recent study by Mosele *et al.* (2021) did not confirm the role of platelets in the pathogenesis of adenomyosis, failing to corroborate the findings of Liu *et al.* (2016).

Abnormal hormone regulation

Adenomyosis is a complex disorder affected by hormone imbalances (Stratopoulou *et al.*, 2021a) and commonly characterized as an estrogen-dependent benign uterine disease. Aberrant expression of ERs, as well as decreased expression of PRs, are reported in both EECs and ESCs of women with adenomyosis (Stratopoulou *et al.*, 2021a; Bulun *et al.*, 2023). Because progesterone opposes estrogenic activity via its receptors, PR deficiency is likely responsible for increased levels of E2 in endometriosis and adenomyosis. This contributes to the hyperestrogenic environment that appears to play a pivotal role in both disease onset and evolution (Mehasseb *et al.*, 2011; Stratopoulou *et al.*, 2021a; Taylor *et al.*, 2021). As in endometriosis (Bulun *et al.*, 2010, 2023; Donnez and Dolmans, 2021), progesterone expression is deficient also in ESCs in adenomyotic tissue compared to normal endometrium, which could lead to progesterone resistance (Liu *et al.*, 2016). A recent study suggested that activating KRAS mutations might be associated with functional progesterone resistance and therefore resistance to progestogen treatment in adenomyosis patients (Inoue *et al.*, 2019). It has also been postulated that estrogen and progesterone signaling act synergistically with the immune response to promote adenomyotic lesion development and progression, with dysregulation of hormone levels resulting in aberrant immune cell accumulation and activity (Bourdon *et al.*, 2021; Donnez *et al.*, 2021).

Crosstalk between ESCs and EECs in adenomyotic lesions

Growth factor trafficking

Several growth factors have been investigated and associated with formation and progression of adenomyotic lesions. Their

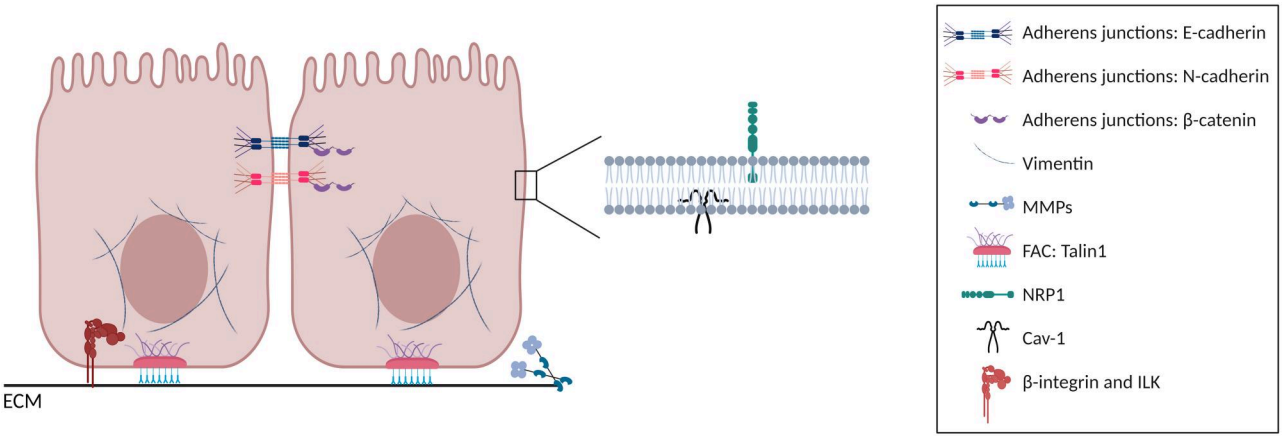


Figure 2. Factors involved in CCM and EMT, found to be relevant in the development of adenomyosis lesions. CCM, collective cell migration; EMT, epithelial-to-mesenchymal transition; Cav-1, caveolin-1; ECM, extracellular matrix; FAC, focal adhesion complex; ILK, integrin-linked kinase; MMPs, matrix metalloproteinases; NRP1, neuropilin-1.

altered expression in endometrial glands and stroma is reported to participate in crosstalk between the two compartments. Overexpression of HGF, a protein involved in regulating cellular processes like cell growth, motility, and morphogenesis, has been detected in glands from the basal endometrium of women with adenomyosis, pointing to a potential role in the pathogenesis of the condition (Khan *et al.*, 2015). NRP1, a transmembrane glycoprotein and coreceptor of VEGF, was found to have strong expression in endometrial cells of women with adenomyosis and is believed to affect the estrogen-dependent aspects of the disorder (Hu *et al.*, 2020). Studies have also revealed upregulation of ILK, a serine/threonine protein serving as the focal adhesion kinase component to the actin cytoskeleton in both eutopic and ectopic endometrium of adenomyosis patients, implying that endometrial cells in this context may acquire invasive features and the ability to escape cell death (Zhou *et al.*, 2018). Abnormal expression of SKP2, an oncogene implicated in invasion and proliferation of cancer cells, was found to be upregulated in EECs and ESCs of women with adenomyosis, suggesting a role in disease development by promoting invasion and proliferation (Guo *et al.*, 2022). Furthermore, adenomyotic lesions exhibit higher levels of hypoxia-inducible factor-1α (HIF-1α) than that found in normal endometrium (Goteri *et al.*, 2009). HIF-1α is a protein activated in hypoxic conditions, including detachment of endometrial glands during the menstrual phase, and is involved in promoting angiogenesis and cellular adaptation to hypoxia. Thanks to these features, it plays an essential role in the physiology of endometrial repair and functional layer regeneration following menstruation. Numerous studies have documented enhanced and/or abnormal vascularization in both eutopic and ectopic endometrium from women with adenomyosis, as well as its participation in disease progression and HMB (Harmsen *et al.*, 2019). Indeed, E2 has notably been found to possibly increase VEGF expression in EECs (Yalaza *et al.*, 2020), thereby promoting angiogenesis (Huang *et al.*, 2014). Altogether, these findings demonstrate that adenomyosis is a complex condition that involves crosstalk and interactions between multiple mechanisms.

Non-coding RNAs

A non-coding RNA (ncRNA) is a type of RNA molecule that functions without being translated into a protein. Zhou *et al.* (2015) conducted a comprehensive analysis of long non-coding RNA (lncRNA) expression in eutopic and ectopic endometrium from adenomyosis patients. Their findings revealed distinct expression patterns of lncRNAs in ectopic endometrium compared to eutopic endometrium in women with adenomyosis. Based on this concept, several studies identified different lncRNAs, such as TUG1, MIR503HG, and miR-191, indicating their involvement in promoting proliferation, migration, and invasion, and hence exacerbating the disorder (Yuan *et al.*, 2022; Xu *et al.*, 2023).

Micro(mi)RNAs (a type of endogenous ncRNA) have also been implicated in epigenetic modifications linked to disease progression. Previous studies of adenomyosis have identified differential expression of several miRNAs, which can control expression of RNA transcripts involved in cellular activities by inducing degradation or suppressing translation at the post-transcriptional level. Studies conducted in recent years have demonstrated that aberrant miRNA expression in endometrial tissues from women with adenomyosis might be involved in cell migration and invasion, promoting faster growth and stronger infiltration by endometrial cells. MicroRNAs like miR-124-3p (Huang *et al.*, 2021a), let-7 (Huang *et al.*, 2021b), miR-10b (Guo *et al.*, 2015) miR-145 (Wang *et al.*, 2021b,c), miR-218 (Zhang *et al.*, 2022), miR-22HG, and miR-2861 (Yu *et al.*, 2021) are commonly involved in cell differentiation and proliferation, and are often reported in the literature to be downregulated in both endometriosis and adenomyosis. Conversely, expression of miRNAs like miR-17 (Hu *et al.*, 2017; Liang *et al.*, 2020), circPVT1 (Wang *et al.*, 2021b,c), and miR-183 (Wang and Chen, 2022) is usually upregulated in endometrial tissues from women with adenomyosis.

To sum up, various ncRNA types have been implicated in the development and progression of uterine adenomyosis. These ncRNAs participate in cell viability, invasion, and apoptosis, contributing to the understanding of molecular mechanisms underlying adenomyotic lesion formation. Nevertheless, their exact role in the pathogenesis needs to be further investigated. The potential functions of ncRNAs in adenomyosis lesion development are summarized in Table 1.

Extracellular vesicles

Extracellular vesicles (EVs), including exosomes, play a crucial role in the transfer of proteins, lipids, and RNA species like miRNAs and circular(circ)RNAs to recipient cells in the microenvironment surrounding the endometrium. These EVs are secreted from endothelial cells, ESCs and EECs, and can act upon the endometrium, inducing changes in its physiological state.

Table 1. Potential functions of non-coding RNAs in the development of ectopic adenomyotic lesions.

References	Non-coding RNA	Non-coding RNA expression	Pathway involved	Alteration observed	Function
Guo *et al.*, 2015	**miR-10b**	↓	ZEB1 and PIK3CA	N/A	Enhance EMT
Huang *et al.*, 2021a	**miR-124-3p**	↓	NRP1	Overexpression of NRP1	Enhance EMT
Lin *et al.*, 2020	**let-7**	↓	Lin28/Let-7a axis	Overexpression of smooth muscle cells in the JZ	Enhance EMT
Yu *et al.*, 2021	**MIR22HG**	↓	STAT3/c-Myc/FAK	STAT3 and MMP-2 upregulation	Promote endometrial cell proliferation
	miR-2861	↓			
Hu *et al.*, 2017 Liang *et al.*, 2020	**miR-17**	↑	lncRNA H19/miR-17	Increased PTEN expression	Promote cell viability and invasiveness
	lncRNA H19	↓		Decreased PTEN expression	Regulate proliferation and induce apoptosis in ESCs
Wang *et al.*, 2021b Wang *et al.*, 2021c	**circPVT1**	↑	miR-145/Talin1 axis	N/A	Promote cell invasiveness
	miR-145	↓			
Wang and Chen, 2022	**miR-183**	↓	miR-183/MMP-9	N/A	Promote cell viability and invasiveness
Xu *et al.*, 2023	**MIR503HGH**	↑	Wnt/β-catenin	Downregulation of E-cadherin and upregulation of N-cadherin	Promote cell viability and invasiveness
	miR-191	↑			Enhance EMT
Yuan *et al.*, 2022	**TUG1**	↑	E2F2/KLF5	ESC migration and aggressiveness	Enhance EMT
Zhang *et al.*, 2022	**miR-218**	↓	LASP1 overexpression	Increased vimentin expression	Enhance EMT

EMT, epithelial-to-mesenchymal transition; ESC, endometrial stromal cells; JZ, junctional zone.

This transfer by EVs is actually a paracrine signaling mechanism from secretory cells to target cells. EVs serve as nano-sized carriers that mediate cell-to-cell or cell-to-environment communication. Recent studies have highlighted their involvement in cancer progression and metastasis by the horizontal transfer of signals between cancer and resident cells (Arena *et al.*, 2023; Yi *et al.*, 2023). In the context of adenomyosis, studies conducted by Chen *et al.* (2020) demonstrated that when EECs are co-cultured with EVs derived from women with adenomyosis, they exhibit enhanced invasiveness and migration, decreased expression of E-cadherin and cytokeratin 19, and increased expression of vimentin and ZEB1. In brief, EVs play a critical role in mediating transfer of RNA species to recipient cells, thereby influencing and promoting the invasive behavior and phenotypic changes of endometrial cells in adenomyosis (Cheng *et al.*, 2023). This supports the notion that EVs can impact disease development, with substantial differences observed between healthy controls and adenomyosis patients, suggesting that EVs and their cargo may be used as diagnostic markers and therapeutic targets for adenomyosis.

Common pathogenic features between adenomyosis and deep endometriotic nodules

The potential link between adenomyosis and endometriosis has been a topic of discussion for many years. Indeed, deep endometriotic nodules are active estrogen-dependent entities characterized by the presence of endometrial glands and scanty stroma within fibromuscular tissue (Nisolle and Donnez, 1997). Deep endometriotic nodules exhibit similar symptoms, molecular aberrations, and histological patterns to adenomyosis, with coexistence rates of up to 97% in nodules over 3 cm in size (Chapron *et al.*, 2017; Donnez *et al.*, 2019, 2024). Like adenomyosis, these nodules feature fibromuscular hyperplasia surrounding foci of glands and stroma, and are more likely to develop into adenomyoma-like tumors (Nisolle and Donnez, 1997), as confirmed in an experimental baboon model developed by Donnez *et al.* (2013). Recent MRI-based studies show increasing evidence of an association between the two diseases, suggesting a potential common origin (Chapron *et al.*, 2017; Donnez *et al.*, 2019). According to Donnez *et al.* (2015), E-cadherin expression is reduced in the invasive part of diseased tissue, strongly indicating that gland invasion is predominantly driven by CCM in deep endometriotic nodules (García-Solares *et al.*, 2018a). Studies conducted in human samples show lower expression of E-cadherin, ERs and PRs in tissue affected by deep endometriotic nodules than normal endometrium, and also higher expression of N-cadherin (Burney *et al.*, 2007; Biyik *et al.*, 2021; Stratopoulou *et al.*, 2021b; Kalkan *et al.*, 2022). By comparing deep endometriotic nodules and adenomyosis side by side, Stratopoulou *et al.* (2021b) identified specific pathogenic features shared by the two diseases, namely a drop in platelet numbers, excess macrophage accumulation, fibrosis, and irregular angiogenesis. Consistent with the theory supporting CCM involvement in endometrial cell migration and invasion, invasive endometriotic lesions showed significantly higher mitotic activity in baboon models compared to noninvasive lesions (Donnez *et al.*, 2015).

Table 2. Commonly pathogenic features of adenomyosis and deep endometriotic nodules.

	References	Characteristics reported	Expression
Adenomyosis	Chen *et al.*, 2010; Zhou *et al.*, 2018	**E-cadherin**	↓
Deep endometriotic nodules	Donnez *et al.*, 2015; García-Solares *et al.*, 2018a		
Adenomyosis	Chen *et al.*, 2010; Zhou *et al.*, 2018	**N-cadherin**	↑
Deep endometriotic nodules	Biyik *et al.*, 2021; Kalkan *et al.*, 2022		
Adenomyosis	Chen *et al.*, 2010; Zhou *et al.*, 2018; Harmsen *et al.*, 2019	**EMT**	N/A
Deep endometriotic nodules	Stratopoulou *et al.*, 2021b		
Adenomyosis	Donnez *et al.*, 2015; García-Solares *et al.*, 2018a; Zhai *et al.*, 2022	**CCM**	N/A
Deep endometriotic nodules	Donnez *et al.*, 2015; García-Solares *et al.*, 2018a		
Adenomyosis	Kitawaki *et al.*, 2001; Mehasseb *et al.*, 2011	**ERs, PRs**	↓
Deep endometriotic nodules	Biyik *et al.*, 2021; Kalkan *et al.*, 2022		
Adenomyosis	Matsumoto *et al.*, 1999; Yang *et al.*, 2007	**Ki67**	↑
Deep endometriotic nodules	Donnez *et al.*, 2015; Orellana *et al.*, 2017		
Adenomyosis	Inoue *et al.*, 2019; Bulun *et al.*, 2021	**KRAS mutations**	N/A
Deep endometriotic nodules	Koppolu *et al.*, 2021		
Adenomyosis	Li *et al.*, 2006; Wang and Chen, 2022	**MMP-9**	↑
Deep endometriotic nodules	García-Solares *et al.*, 2018a		
Adenomyosis	Guo *et al.*, 2015	**miR-10**	↓
Deep endometriotic nodules	Haikalis *et al.*, 2018		

EMT, epithelial-to-mesenchymal transition; CCM, collective cell migration; ER, estrogen receptor; PR, progesterone receptor; N/A, not available.

Ki67 was also found to be significantly more extensive at the invasion front than in the center of lesions (Orellana *et al.*, 2017). Moreover, somatic mutations were detected in deep endometriotic lesions, particularly in epithelial glands. Building upon these observations, recent studies have identified recurrent KRAS mutations and dysregulated genes commonly involved in the pathogenesis of deep endometriotic nodules (Koppolu *et al.*, 2021; Bulun *et al.*, 2023), providing further evidence of the involvement of genetic factors in the pathophysiology of both deep endometriotic nodules and adenomyosis. With respect to ECM remodeling, García-Solares *et al.* (2018a) found significantly stronger MMP-9 expression in glands and stromal cells at the invasion front than in the center of deep nodular endometriotic lesions, making it the first study to demonstrate increased expression of this protease throughout the invasion process of deep endometriotic lesions. These findings firmly support the role of MMP-9 in the development and progression of the disease, as was very recently demonstrated for adenomyosis (Stratopoulou *et al.*, 2023). Table 2 reports common pathogenic features of both adenomyosis and deep endometriotic nodules typically described in the literature.

The abundance of publications on adenomyosis and deep endometriotic nodules is at odds with the lack of investigations into the association between these two pathologies. There is a huge need for comprehensive studies looking to understand events that take place in the microenvironment of the uterus to be able to characterize the pathogenic mechanisms that contribute to the cause and development of these enigmatic diseases. Further research should also be conducted to clarify EV-mediated crosstalk between endometrial cells, elucidate the role of miRNA alterations in both conditions and explore any similarities or shared molecular pathways.

Conclusion

The literature has shed light on new actors in the establishment and progression of adenomyosis and deep endometriotic nodules, including biological changes in migration potential (CCM), cell features (EMT), and survival abilities of the two endometrial compartments, namely stromal cells and epithelial glands. Ectopic cells in endometriotic and adenomyotic tissue exhibit resistance to apoptosis and autophagy, allowing them to survive and proliferate abnormally. MMP-mediated ECM degradation along with enhanced angiogenesis facilitates cell motility and may play a significant role in the pathogenesis of adenomyosis and deep endometriotic nodules. Notably, abnormal hormone regulation, such as hyperestrogenism and progesterone resistance, are crucial factors in the development of both conditions and their associated symptoms. In case of adenomyosis, it has been observed that macrophages rather than platelets initiate this process, ultimately leading to progression of lesions and fibrogenesis. Although these diseases were first described more than a century ago, controversy still surrounds their pathogenesis. The main limitation lies in the variability and lack of specificity of clinical manifestations of both endometriosis and adenomyosis, often leading to delayed diagnosis. This complicates investigations into early disease stages and less severe presentations, which are frequently asymptomatic and therefore underdiagnosed. Considering what we already know, future research should focus on gathering more precise and comprehensive phenotypic data on epithelial glands and stromal cells within lesions to pave the way for more targeted therapeutic approaches for these conditions. However, identifying the exact mechanisms underlying the development of adenomyosis and deep endometriosis presents considerable challenges for gynecologists, endocrinologists, and researchers alike. Gaining a

fundamental understanding of the events taking place in the microenvironment of the uterus is essential to fully characterize the different pathogenic mechanisms that contribute to initiation and progression of these two diseases and to establish the link between them. Researchers must delve into the complex molecular and cellular crosstalk between ESCs and EECs that drives development of these disorders, investigating the role of various signaling pathways, as well as examining how these pathways interact with ncRNAs released by EVs.

Data availability

This is a review article. Therefore, no new data were generated.

Authors' roles

M.Z.: original draft writing and conceptualization. L.C.: manuscript review and editing. M.-M.D.: supervision, manuscript review and editing.

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Conflicts of interest

The authors declare no competing interests.

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