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REVIEW

Origin and Pathogenic Mechanisms of Uterine Adenomyosis: What Is Known So Far

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Abstract

Uterine adenomyosis is a benign disease, commonly encountered in reproductive-age women and responsible for chronic pelvic pain, abnormal uterine bleeding, and infertility. Although the exact origin and pathogenic mechanisms involved in adenomyosis still need to be elucidated, significant progress has been made over recent years. Ever since the theory of endometrium invaginating the myometrium via a traumatized interface was first proposed, numerous molecular mechanisms have been reported to participate in this process. At the same time, an alternative theory has suggested de novo development of adenomyotic lesions from metaplasia of Müllerian remnants or adult stem cells. Hence, our understanding of the pathogenesis of adenomyosis has been greatly enhanced and is anticipated to pave the way for development of an effective and safe treatment. The goal of this review is to analyze current knowledge on the origin and pathogenic mechanisms of adenomyosis, ranging from the most widely accepted theories to newly reported data.

Keywords Adenomyosis · Pathogenesis · Invagination · Metaplasia · Disease mechanisms

Introduction

Adenomyosis is a compound word, etymologically deriving from the Greek terms aδénas (αδένας), meaning gland, and mís (μυς), meaning muscle, and referring to a pathological condition of the muscle involving glands. Even though the term "adenomyosis uteri" dates back to 1925 [1], the current definition is largely based on a 1972 publication, when Bird et al. defined adenomyosis as "benign invasion of endometrium into the myometrium, producing a diffusely enlarged uterus which microscopically exhibits ectopic, non-neoplastic, endometrial glands and stroma surrounded by hypertrophic-hyperplastic musculature" [2]. Today, adenomyosis is commonly described as an estrogen-dependent benign uterine disease, characterized by the presence of endometrial tissue penetrating the myometrium to a depth of at least 2.5 mm at the time of histological diagnosis, and often surrounded by hyperplastic and hypertrophic smooth muscle [3, 4]. Based on the distribution pattern of lesions inside the myometrium, adenomyosis is characterized as focal when a nodular collection is identified, or diffuse when glands and stroma are dispersed throughout the myometrium [3, 5]. Besides distinct histological patterns, these two forms of adenomyosis have been found to present with different degrees of symptoms, infertility, and association with endometriosis [5]. Alternatively, in some adolescents and young adults, adenomyosis can develop into a large cyst, known as a cystic adenomyoma [6].

The diagnosis of adenomyosis has long troubled clinicians, as its symptomatology varies in severity and overlaps with other uterine diseases, like endometriosis and leiomyomas [7, 8]. In addition, adenomyosis frequently coexists with these diseases, further complicating the clinical diagnosis [8]. Recent improvements in imaging techniques, such as transvaginal ultrasonography (TVUS) and magnetic resonance imaging (MRI), have somewhat facilitated its diagnosis, thereby allowing major advances in the field [7, 8].

It is nevertheless impossible to accurately estimate the prevalence of the disease, primarily due to its challenging

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diagnosis, but it is clear that adenomyosis is one of the major pathologies that gynecology clinics deal with on a daily basis, with an estimated prevalence of 20–30% [9–11]. In previous decades, adenomyosis was thought to affect almost exclusively women in their forties and fifties, often multiparous. This belief was partially due to the fact that the diagnosis was generally confirmed upon hysterectomy, and younger, nulliparous women often think twice before undergoing such drastic sterilizing surgery [10, 12]. These days, TVUS is the method of choice, allowing noninvasive diagnosis of adenomyosis and revealing its true incidence [8]. In fact, a prevalence of 24.4% was reported in women attending assisted reproduction clinics [13], while another study recorded diffuse adenomyosis, diagnosed by TVUS, in 34% of examined nulligravid young adults (18–30 years of age) [14]. The presence of adenomyosis in this population was associated with chronic symptoms, emphasizing the importance of adenomyosis diagnosis and management in younger women [14].

Typical symptoms of adenomyosis include intense chronic pelvic pain, abnormal uterine bleeding, and infertility, although some patients are asymptomatic [7]. Despite not being a fatal disease, growing evidence points to potentially severe health complications. A recent study including 876 gynecological patients demonstrated an elevated risk of ovarian and endometrial cancer development in women with a history of adenomyosis, unlike other benign uterine diseases, such as endometriosis or leiomyomas [15]. A large study of 486,077 participants, investigating the likelihood of patients with adenomyosis developing different forms of cancer, reported increased susceptibility to endometrial and thyroid cancer compared to adenomyosis-free women [16]. Other studies revealed pathological characteristics of undiagnosed adenomyosis in hysterectomy samples from women with endometrial cancer at rates of 28% and 41% of 229 and 1399 cases respectively [17, 18], while the corresponding percentage for endometriosis was considerably lower [18]. Endometrial cancer actually arising from adenomyotic lesions is also a rare but serious complication, as reviewed by Habiba et al., who found 78 such case reports in their recent 20-year systematic review [19]. Despite the lack of conclusive evidence regarding the nature of this correlation, it is safe to assume that adenomyosis is a complex and occasionally dangerous disease that requires cautious handling by health care professionals.

Although the high prevalence and severity of the disease are known, its pathogenesis is not yet completely understood, so there are no drugs available to specifically treat adenomyosis [6, 19]. Pharmacological options include mostly hormonal and anti-inflammatory agents, aiming to temporarily suppress estrogen production, relieve pain, and improve fertility [20]. In a review by Vannuccini et al., gonadotropin-releasing hormone (GnRH) analogs, progestins, GnRH antagonists, and selective progesterone receptor modulators (SPRMs) were discussed as popular options [20], but GnRH agonists have been linked to significant side effects and cannot be used for long periods, while the efficacy of SPRMs as medical therapy for adenomyosis has been in question since 2016 [21]. Interestingly, a recent case report compared the efficacy of these two treatments, namely SPRMs and GnRH antagonists, in a patient with severe adenomyosis [22]. In 2017, the patient was given an SPRM that exacerbated her symptoms. Two years later, GnRH antagonist (linzagolix) was administered, resulting in rapid uterine volume reduction and lesion regression, highlighting the potential of this type of treatment [22].

The gold standard for management of adenomyosis remains hysterectomy [3], which comes with a risk of complications and postoperative morbidity, as well as effectively ending a patient's fertility prospects. Increased diagnoses, including in younger patients [6, 13, 14], combined with the growing trend to delay the first pregnancy, drive home the importance of understanding the mechanisms behind adenomyosis development and related symptoms. The aim of the present manuscript was to review the most popular hypotheses on the origin and mechanisms involved in the development of adenomyosis, including the latest reports.

Hypotheses on the Origin of Adenomyosis

Even though the origin of adenomyotic lesions remains unclear, two main theories have been investigated over the years: (1) invagination of the endometrial basalis into the myometrium as a result of constant activation of the tissue injury and repair (TIAR) mechanism; and (2) metaplasia of misplaced pluripotent Müllerian remnants or differentiation of adult stem/progenitor cells [3, 7] (Fig. 1).

Invagination of the Endometrial Basalis into the Myometrium upon TIAR Activation

The most widely accepted theory on the origin of adenomyosis suggests invagination of the endometrial basalis into the myometrium due to repeated TIAR activation [23]. According to the invagination theory, the hyperestrogenic environment of the uterus causes chronic contractions of the myometrium, with subsequent trauma to the endometrial-myometrial junctional zone (JZ) (also known as the endometrial-myometrial interface) [24, 25]. More specifically, initial mechanical stress on the JZ activates cyclooxygenase-2 (COX-2), resulting in production of prostaglandin E_2 (PGE_2) and hence further intensifying the stress [23]. The TIAR mechanism is then triggered in response to the trauma and more estrogen is produced locally, further increasing uterine contractility. As a result, a vicious cycle of estrogen

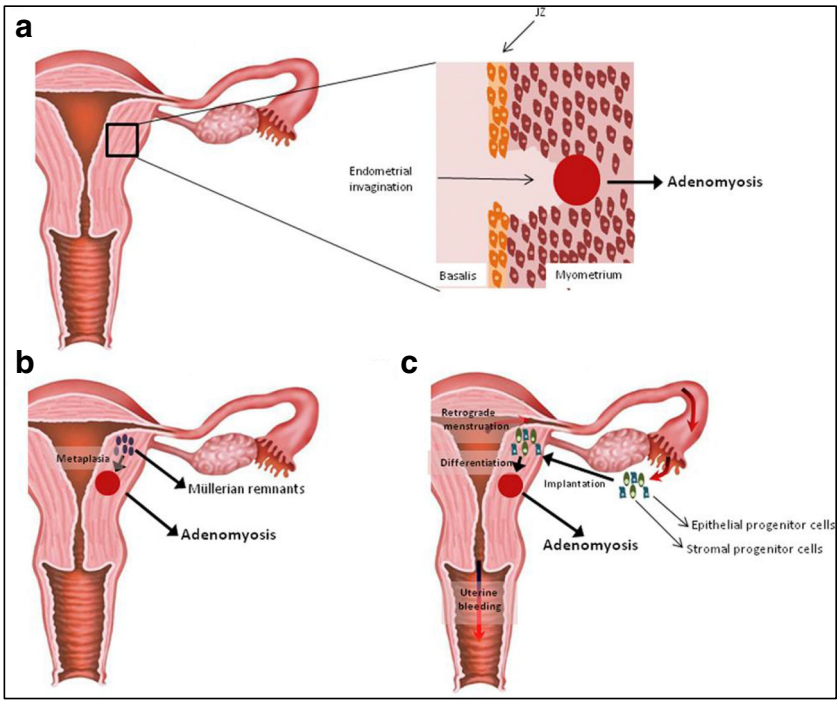

Fig. 1 Hypotheses on the origin of adenomyosis. **a** Invagination of the endometrial basalis into the myometrium. **b** Differentiation of embryonic Müllerian remnants. **c** Implantation and differentiation of blood-derived stem cells upon retrograde menstruation (figure from ref. [3])

production, wound healing, and auto-traumatization commences [3, 23]. Alternatively, initial injury to the JZ may result from iatrogenic trauma, considered a risk factor for adenomyosis development [12, 24]. Surgical interventions like dilation and curettage or cesarean section could trigger a rapid tissue repair response, with subsequent local estrogen production and uterine hyperperistalsis [24]. Upon initiation of the disease, the myometrium is invaded by endometrial tissue due to the traumatized JZ, which is a crucial step in establishing its pathogenesis (Fig. 2).

Indeed, a disrupted JZ may provide a reasonable explanation of how endometrial tissue is able to invade the myometrium. It has been shown that uteri of adenomyosis patients exhibit hyperperistalsis and dysperistalsis, especially in case of a diffuse phenotype [25]. To accept this explanation, however, it is important to elucidate the initial trigger (if any) for the hyperestrogenism that drives this mechanism. To this end, potential abnormalities in estrogen synthesis, action, and catabolism in adenomyosis have been the subject of numerous studies. Abnormal estrogen metabolism may be involved, as both mRNA upregulation and differences in genetic variants of aromatase cytochrome P450 (CYP19) have been reported in adenomyosis [26, 27]. This gene encodes cytochrome P450, a major component of the aromatase complex, which catalyzes the

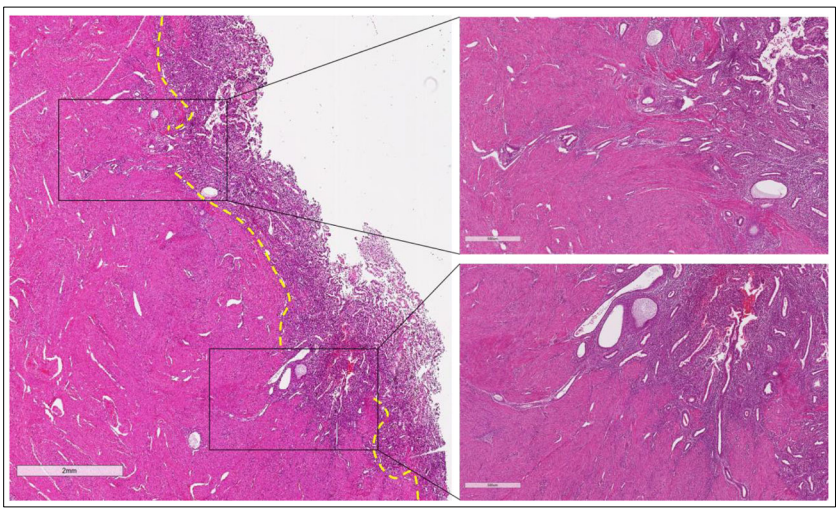

Fig. 2 Histological appearance of adenomyosis initiation. The JZ (yellow line) is disrupted and basal endometrial tissue invades the myometrium

conversion of androgens to estrogens. Its upregulation or altered function could therefore lead to aberrant local estrogen production.

Alternatively, differences in estrogen function might ensue from differential expression of its receptors in the uterus, namely estrogen receptor alpha (ER-α) and estrogen receptor beta (ER-β). Polymorphisms in the ER-α gene might be implicated, as different variants of the locus were found predominantly in women with adenomyosis compared to disease-free subjects [28]. Abnormal expression of ER-α, inconsistent with physiological cyclic changes, has also been reported in adenomyotic endometrium and lesions, associated with a decrease in myometrial expression of progesterone receptor alpha (PR-α) and progesterone receptor beta (PR-β) [29]. Considering that progesterone opposes estrogenic action via its receptors, decreased PR expression could be another indication of hyperestrogenism in adenomyotic uteri. In fact, progesterone resistance in adenomyotic endometrium is considered to be another characteristic of adenomyosis, identified as far back as 1997 [30]. Nisolle and Donnez first reported this phenomenon, suspecting a dysregulated mechanism of PR expression, or even present but inactive receptors [30]. More recently, decreased expression of PR-β in adenomyotic lesions was recorded as the underlying cause of progesterone resistance, thought to be epigenetically regulated [31–33].

The pivotal role of these mechanisms in adenomyosis is highlighted by the fact that most mainstream treatments for adenomyosis directly or indirectly interact with estrogen and progesterone, as already stated. Previously reported data demonstrate the primordial role of estrogen concentrations in the pathophysiology of the disease, suggesting that managing estrogen levels with GnRH antagonists could even partially replace surgery for adenomyosis treatment [22].

De Novo Development of Ectopic Endometrium from Displaced Embryonic Müllerian Remnants or Adult Stem Cells

While the invasion hypothesis is the most widely accepted theory among the scientific community, it is also possible that adenomyotic lesions arise de novo from metaplasia of displaced embryonic pluripotent Müllerian remnants or differentiation of adult endometrial stem cells (EnSCs) [3]. Indeed, the premise of a structure composed of embryonic Müllerian tissue incorporated inside normal organs during organogenesis (or Müllerianosis) was previously used by Batt et al. to explain the developmental origin of both adenomyosis and endometriosis [34]. Batt supported his theory with cases from the literature, in which organoid structures of "primitive endometrial tissue" were identified in fetuses or newborns [34]. Further evidence was provided by Signorile et al., who detected displaced endometrial tissue in fetuses in different ectopic locations, including the posterior wall of the uterus [35].

The hypothesis of Müllerianosis in developmental adenomyosis has not been sufficiently studied to draw any robust conclusions, nor does it explain the existence of diffuse adenomyosis, which is usually the case. However, it should not be ruled out, since rare cases of adenomyosis in women with Rokitansky-Küster-Hauser syndrome (absence of functional endometrium) allude to the existence of a different pathogenic invagination mechanism, at least in certain cases [36, 37].

On the other hand, it is possible that development of endometrial tissue inside the myometrium is an outcome of differentiation of adult stem/progenitor cells residing in the uterus [3]. Indeed, the ability of just a small part of the endometrium to regenerate the entire functional layer has long puzzled and excited researchers. It is safe to assume that all progenitor cells required for this repeated regeneration are located inside the basal layer and can reform glands, stroma, and the endometrial vasculature [38]. Although the regenerative capacity of the endometrial basalis has long been known, the first convincing evidence of cells with clonogenic potential in the human uterus dates back to 2004, when Chan et al. observed the clonogenic ability of stromal and epithelial cells isolated from the basalis of adult patients undergoing hysterectomy [39]. That observation paved the way for more extensive research in the field. Today, EnSCs are well-characterized cell populations which, thanks to their known markers, can be easily purified from tissue or menstrual blood via routine cell isolation techniques.

Adult stem or progenitor cells differentiating into ectopic endometrial tissue can also relate to Sampson's hypothesis of retrograde menstruation in the pathogenesis of endometriosis [39, 40]. Sampson suggested that endometriosis arises from endometrial cells in menstrual blood implanting outside the uterus during retrograde menstruation, but did not explain why not all women with retrograde menstruation develop endometriosis [40]. In this scenario, menstrual blood–derived stem cells (MenSCs) that have been detected and characterized in menstrual blood might implant inside the pelvic cavity during retrograde menstruation and differentiate to form endometrial tissue [41, 42]. Differences in numbers and characteristics of MenSCs resident in menstrual blood between women may determine the development or not of ectopic lesions [42]. Even though this concept has only been used to explain endometriosis, MenSCs may be deposited into the myometrium and eventually differentiate into endometrial glands and stroma, creating de novo adenomyotic foci in a similar manner [3].

Mechanisms of Adenomyotic Lesion Development and Disease Progression

The mechanisms underlying adenomyosis development are still a mystery, with the abovementioned hypotheses showing

potential but also limitations. Nevertheless, our understanding of both cellular and molecular factors involved in adenomyosis establishment has dramatically increased over the recent decades (Fig. 3), and we are now looking to elaborate on some of these mechanisms.

Cell Proliferation and Apoptosis

Over-proliferating endometrial cells escaping programmed cell death is not a new concept to explain adenomyosis pathogenesis. More than 10 years ago, the team of Yang et al. reported increased rates of proliferation and decreased levels of apoptosis in primary cultured endometrial stromal cells (ESCs) derived from the endometrium of adenomyosis patients [43]. A more recent publication reported upregulation of B cell lymphoma 2 (Bcl-2) mRNA and protein in eutopic endometrium from adenomyosis patients, indicative of resistance to apoptosis [44]. When the authors silenced the Bcl-2 gene in cultured eutopic ESCs, they observed a negative impact on the viability and migration capacity of the cells, along with increased apoptosis, further confirming its important role [44].

Elevated proliferative activity has also been reported in ectopic endometrium from adenomyosis patients compared to controls, as demonstrated by immunohistochemistry analysis for proliferating cell nuclear antigen [32]. An alternative cancer-like mechanism of reduced apoptosis in adenomyosis has been suggested too, relying on downregulation of the tumor suppressor GRIM-19 [45]. In a study by Wang et al., GRIM-19 was found to be significantly downregulated in ectopic endometrium from adenomyosis patients, while modifications in its expression in cultured Ishikawa cells altered expression of active phosphorylated signal transducer and activator of transcription 3 (pSTAT3) and vascular endothelial growth factor (VEGF), pointing to a signaling cascade of these molecules in adenomyosis pathogenesis [45]. Taken together, these data suggest an important role for over-proliferation combined with impaired apoptosis in adenomyotic lesion establishment and progression.

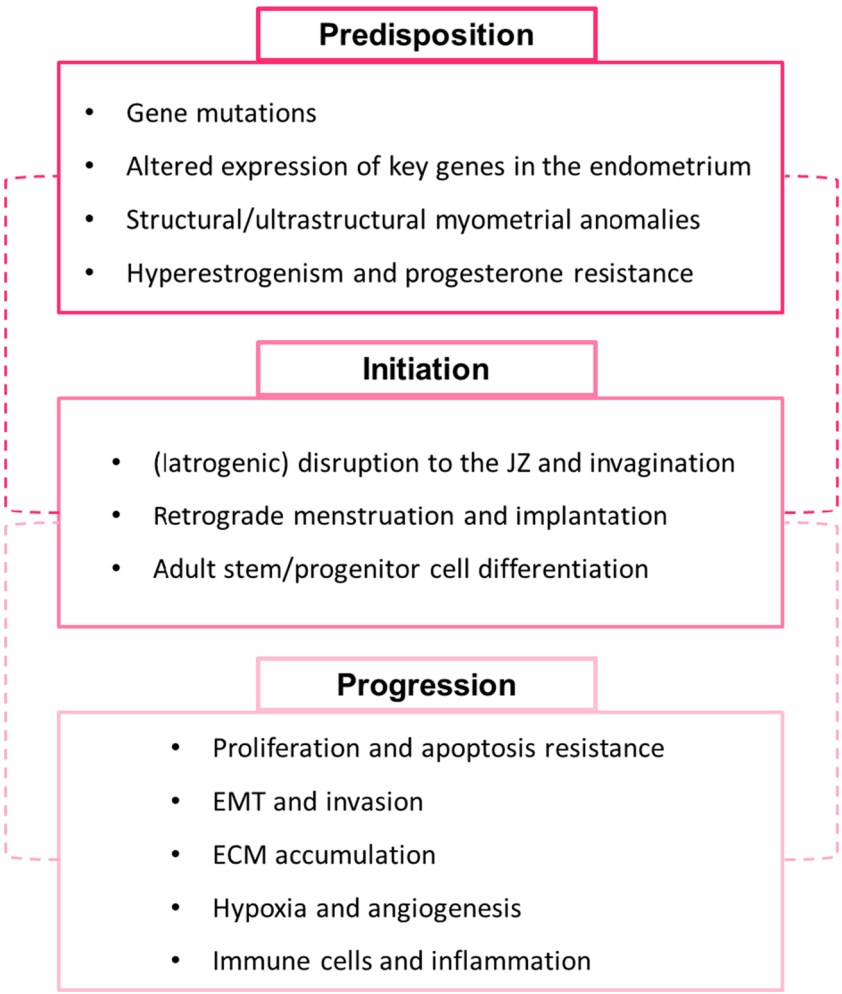

Fig. 3 Summary of proposed mechanisms behind adenomyosis predisposition, initiation, and progression

Epithelial to Mesenchymal Transition (EMT) and Fibroblast to Myofibroblast Transdifferentiation (FMT)

Upon initiation of the disease, invasion of the myometrium by endometrial tissue is crucial for establishment of adenomyosis (Fig. 2). It has been suggested that EMT is a key event boosting the migratory and invasive capacity of adenomyotic lesions [46]. More specifically, abnormal wound healing responses in the uterus lead to overactivation of the transforming growth factor beta 1 (TGF-β1)/SMAD3 pathway, resulting in both EMT and FMT, with endometrial cells acquiring invasive capacities [47, 48]. EMT is characterized by destabilization of cell-cell junctions, loss of apico-basal polarity, a switch from epithelial-expressed genes to mesenchymal, and eventually transition into mesenchymal cells with motile capacity [48]. This process is essential to normal development and wound healing, but it is pathologically implicated in cancer progression and fibrosis [48]. Fibrosis, another consequence of an abnormal healing response, is the outcome of transdifferentiation of fibroblasts into extracellular matrix (ECM)–producing myofibroblasts [48]. Fibrosis has been reported in adenomyotic stroma and in perivascular locations inside the myometrium, and may or may not be TGF-β1/SMAD3-dependent [31, 32, 49]. Excess ECM deposition impairs normal tissue function and may be responsible for the intense pelvic pain felt by adenomyosis patients [49].

Indeed, as the endometrial basalis is in close contact with the JZ, without any intervening membrane, invasive mesenchymal cells could easily migrate into the myometrium. EMT was first reported in adenomyosis in a 2010 study, where the authors observed the downregulation of E-cadherin in association with upregulation of vimentin in the epithelial compartment of adenomyotic lesions, a typical characteristic of EMT [46]. Moreover, subsequent in vitro experiments showed that changes to gene expression, along with acquisition of cell migration capacity, were estrogen-dependent, as blocking estrogen signaling completely eliminated these effects [46]. Since then, a number of factors (TGF-β1, hepatocyte growth factor, focal adhesion kinase, integrin-linked kinase, and neuropilin-1) have been suggested as potential regulators of the EMT process in adenomyosis [32, 50–53]. Cells that typically secrete or interact with these factors, namely platelets and macrophages, have also been investigated [32, 54].

Platelets, well-known coagulation inducers, have been proposed as regulators of physiological endometrial repair, as they were detected in healthy menstrual endometrium, but not during the other two phases of the cycle [55]. Activated platelets were recently suggested to be potential mediators of EMT and FMT in adenomyotic lesions by triggering the TGF-β1/SMAD3 cascade [12, 32]. The authors reported platelet aggregation in adenomyotic lesions, but not in control samples from unaffected uteri [32]. Platelet aggregation was associated with typical EMT and FMT marker upregulation, and increased content of thick collagen fibers consistent with fibrosis was also observed [32]. A more recent study, however, failed to confirm the role of platelets, as anti-CD41 immunostaining found no platelet aggregation in adenomyotic lesions [Mosele et al., submitted for publication]. In the same study, dense collagen fibers consistent with fibrosis were seen in adenomyotic stroma, indicating the possible existence of a platelet-independent mechanism of FMT that needs to be further investigated.

Angiogenesis in Adenomyotic Lesion Establishment

Ectopic endometrium in adenomyosis, like eutopic and healthy endometrium, undergoes cycling bleeding, shedding tissue pieces including the vessels. It is reasonable to assume that here is a mechanism of endometrial repair in ectopic endometrium too, which restores the vasculature via formation of new vessels. Numerous studies have reported enhanced and/or abnormal vascularization in both eutopic and ectopic endometrium from patients with adenomyosis, as well as its involvement in disease progression, heavy bleeding, and impaired embryo receptivity [56]. On the other hand, some antiangiogenic properties have been reported in adenomyosis, namely downregulation of the potent angiogenic factors interleukin-10 and E-cadherin, suggesting a potentially abnormal angiogenesis mechanism [32, 57].

VEGF is a potent endothelial cell mitogen secreted in the endometrium by epithelial, stromal, and perivascular cells, as well as other cells involved in endometrial repair like macrophages [58]. VEGF is essential for normal endometrial repair in menstruation, but has been found to be upregulated in adenomyotic lesions [32, 59, 60] and their corresponding endometrium [60]. During menstruation, hypoxia-inducible factor 1alpha (HIF-1α), a major transcription factor activated by hypoxia and its target VEGF, participates in endometrial repair and angiogenesis [61]. Hypoxia might be typical of adenomyosis, resulting from an injured JZ, with subsequent damage to vessels and loss of blood perfusion [12, 59]. Indeed, abnormal expression of HIF-1α has been reported in adenomyosis and may cause adenomyosis progression and heavy menstrual bleeding [59, 61].

Microvessel density (MVD) serves as another frequent marker of angiogenesis, especially in tumors, and is calculated as the number of (small) vessels in a defined area. Increased MVD has been recognized as meaningful in adenomyotic lesions and eutopic endometrium for more than two decades now [32, 62, 63]. One study evaluated MVD in adenomyosis by immunohistochemistry for CD34, a marker of endothelial cell proliferation and motility during angiogenesis [63]. The authors observed enhanced CD34 immunostaining in ectopic endometrium from adenomyosis patients compared to corresponding eutopic and control endometrium. However, they did not encounter any significant difference in MVD between

eutopic and control endometrium, in contrast to the earlier study by Ota et al. [62, 63]. Overall, these findings support the involvement of enhanced and/or abnormal angiogenesis in adenomyosis pathogenesis, but further research is needed to shed light on its exact cause and role.

Involvement of Immune Cells

The concept of adenomyosis being an immune disease dates back to 1998 [64], albeit not well documented. It is known that normal endometrium hosts a variety of immune cells that increase in number during the perimenstrual period to ensure successful tissue repair [65]. Considering the variety of functions and secreted factors of these cells in the uterus, it is highly probable that they also play a role in uterine pathologies. Moreover, the increased vasculature described in adenomyosis could facilitate local influx of monocytes and other blood cells.

Macrophage accumulation has been reported to be greater in eutopic endometrium from adenomyosis patients than in healthy controls [57, 66]. Macrophages are crucial to all physiological tissue repair processes, including inside the endometrium, where they release various pro- and anti-inflammatory chemokines, growth factors, matrix metalloproteinases (MMPs), and adhesion factors, depending on the menstrual phase and the presence or absence of an embryo [65, 67]. Before menstruation, endometrial macrophages increase in number and release factors like MMPs, inducing vessel breakdown in the endometrial functionalis [65]. Upon cessation of menstruation, local macrophages acquire proangiogenic properties and release VEGF and endothelial cell–stimulating cytokines in order to restore the lost vascularization [65]. However; continuous macrophage infiltration, as observed in adenomyotic endometrium, can lead to EMT and fibrosis, while secreted inflammatory mediators in the uterus might interfere with other normal functions, like embryo implantation [54, 57, 66, 67].

As mentioned above, macrophages have been investigated as mediators of EMT in adenomyosis, leading to endometrial cells invading the myometrium. Chronic trauma to the JZ would lead to continuous infiltration of the site of injury by inflammatory macrophages [67]. However, a series of in vitro studies demonstrated that activated macrophages co-cultured with both adenomyotic and unaffected endometrial cells induced EMT-like features in these populations, such as down-regulation of the epithelial markers cytokeratin 7 and E-cadherin, upregulation of the mesenchymal markers vimentin and N-cadherin, and invasive capacities of semipermeable membranes [54, 68]. Indeed, the observation of macrophage-induced EMT in primary cell cultures of endometrial cells from both adenomyosis-affected and unaffected women led the authors to speculate that activated macrophages might be the only precondition needed to trigger this mechanism.

On the other hand, it has been suggested that immunotolerance of endometrial debris to natural killer (NK) cell cytolytic activity may be characteristic of adenomyosis [69, 70]. One study reported aberrant expression of human leukocyte antigen-G (HLA-G) protein in eutopic and ectopic endometrium of adenomyosis patients [69]. This protein is physiologically linked to immunotolerance to NK and cytotoxic T cells, indicating resistance of endometrial cells to cytolysis and thus allowing myometrial infiltration [69]. Consistent with this conclusion, another study argued for possible resistance of adenomyotic cells to NK cell activity, as levels of HLA class I and II expression were lower in endometrial specimens from women affected by adenomyosis compared to endometriosis and unaffected subjects [70]. These findings suggest that escaping physiological NK cells activity may be a precondition for successful invasion of the myometrium by endometrial cells [69].

Role of a Predisposed Myometrium

As already stated, hyperperistalsis and dysperistalsis are typical characteristics of adenomyotic uteri and may govern invasion of the myometrium by endometrial tissue [25]. According to Leyendecker et al., uterine peristalsis is the only precondition required to initiate auto-traumatization and subsequent TIAR activation [23]. Based on an MRI study, it was also hypothesized that mechanical stress is accumulated over the years due to chronic peristaltic waves of a non-pregnant uterus, hence provoking an inflammatory response and proliferative activity in adjacent basal endometrium [71]. Moreover, adenomyotic lesions may themselves inflict further mechanical stress while expanding. As a consequence, the TIAR mechanism would be activated in multiple sites simultaneously, exacerbating abnormal endometrial proliferation [71].

Although critical to understanding adenomyosis development, this theory lacks experimental proof. Furthermore, if adenomyosis were initiated exclusively by physiological mechanical stresses in the uterus, there should be some explanation as to why only a few women go on to develop the disease. It would be logical that an underlying myometrial defect would have to contribute to the hypercontractility and facilitate translocation of the basal endometrial glands. Structural or ultrastructural anomalies of myometrial cells appear to be involved in this [72, 73]. One study compared the ultrastructure of uterine myocytes between women with adenomyosis and healthy controls by transmission electron microscopy (TEM), and determined multiple abnormalities consistent with hypertrophy, an imbalance in cytoskeletal component synthesis and turnover, and abnormal uterine contractility, a characteristic of adenomyosis [72]. Another TEM-based study showed various irregularities in adenomyotic uteri, such as a disrupted JZ with basal glands entering the myometrium, smooth muscle cells surrounding several endometrial glands, and abnormally

arranged myocytes in the inner myometrium [73]. The authors correlated their findings with adenomyosis-induced hyperperistalsis and the subsequent trauma [73], thus providing a probable explanation of events in the myometrium that allow adenomyosis initiation.

On the other hand, an underlying condition inducing dysperistalsis and exacerbating mechanical stress on the JZ could explain adenomyosis development in certain women. It was recently demonstrated that chronic endometritis may be the cause of uterine dysperistalsis throughout the menstrual cycle, resulting in trauma to the JZ [74]. While there are insufficient data to claim that this is also the case with adenomyosis, chronic endometritis has already been associated with endometriosis, having been detected in 52.94% of women diagnosed with endometriosis, but only 27.02% of disease-free women [75]. Moreover, distinct microbiotic populations were found predominantly in the uterus of endometriosis and adenomyosis patients compared to healthy controls, suggesting involvement of these microorganisms in disease development [76].

To conclude, myometrial defects appear to play an important role in uterine dysperistalsis and adenomyosis initiation, whereas phenotypic anomalies of myometrial cells, chronic inflammation, or specific uterine microbiotic populations may favor continued development of the pathology.

Genetic Background Favoring Adenomyosis Development

Several attempts have been made to elucidate the potential genetic background of adenomyosis development. Indeed, numerous mRNAs have been found to be dysregulated between healthy and eutopic endometrium from adenomyosis patients. One such attempt was published in 2016, where microarray analysis revealed a total of 1024 mRNAs and miRNAs with differential expression between healthy and eutopic endometrium from adenomyosis patients [77]. Dysregulated genes belonged to pathways involved in proliferation, apoptosis, sex steroid signaling, and ECM remodeling, including several MMPs [77]. A more recent study based on transcriptome sequencing further confirmed the hypothesis of differentially expressed genes in the eutopic endometrium of adenomyosis patients, detecting a total of 373 differentially expressed mRNAs [78]. As expected, pathway analysis showed cell growth, proliferation, and motility to be the most enriched pathways in adenomyosis [78]. Both of these studies, however, are limited by the small number of samples and the origin of the investigated tissue, which came only from the endometrial functionalis, even though adenomyosis is widely believed to originate from the basalis.

A recent study based on next-generation sequencing technology identified recurrent Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations in adenomyotic lesions and corresponding endometrium, concluding that adenomyosis might in fact be an oligoclonal disease associated with mutations in the KRAS gene [79]. KRAS is a proto-oncogene and mutations in this locus have been repeatedly linked to endometrial cancer, especially estrogen-sensitive forms of the disease [80]. Taken together, these studies, combined with the irregularities seen in expression of genes related to estrogen signaling in the uterus, support the hypothesis of a genetic predisposition to adenomyosis.

Common Pathogenesis of Adenomyosis and Deep Endometriosis

The possible relationship between adenomyosis and endometriosis has been a matter of debate for decades. Deep endometriotic nodules (DENs), in particular, seem to share symptoms and histological patterns with uterine adenomyosis, while rates of coexistence as high as 97% have been noted for nodules larger than 3 cm [30, 81]. In an MRI-based study by Chapron et al., it was reported that what the authors called focal adenomyosis of the outer myometrium (FAOM) was significantly correlated with the presence of DENs, while the majority of patients with DENs (66.3%) had concurrent FAOM [82]. On the other hand, this correlation was not observed in the case of diffuse adenomyosis, which was reported in 34.6% of patients included in the study, irrespective of the presence or absence of DENs [82]. These results led the authors to suggest that diffuse adenomyosis and FAOM may be two separate pathological entities, with the latter associated with the presence of DENs, and more specifically the outcome of DEN progression [82]. Indeed, this distinction between FAOM and diffuse adenomyosis is in line with the observation that the two forms of the disease differ significantly in the severity of presented symptoms [5].

In another MRI-based study, Donnez et al. reported external adenomyosis (located in the outer myometrium) in 97/100 of patients with DENs measuring ≥ 3 cm [81]. The authors gave an alternative explanation for this correlation; adenomyosis of the posterior uterine wall or cervical wall may be the source of nodules invading the rectovaginal space; hence, adenomyosis and DENs may actually be two different forms of the same disease [81].

Recent findings on a cellular level appear to point in the same direction. A study compared internal and external adenomyotic lesions with concurrent DENs, in terms of Ber-EP4 (epithelial cell marker), CD10 (stromal cell marker), and other selected adenomyosis-related characteristics [83]. It was shown that Ber-EP4 and CD10 expression patterns, as well as dense collagen fiber content, differed between internal and external lesions, with the latter resembling those of DENs [83]. Based on these common histological patterns between the two types of lesions, it can be assumed that they also have

a common origin [83], although more extensive research is required to prove this notion. Another team investigating the fibrotic process in internal and external adenomyosis reported evidence of the TGF-β1 signaling cascade, along with dedifferentiated smooth muscle cells, only in patients with concurrent external adenomyosis and pelvic endometriosis [84]. They went on to suggest that the origin of fibrosis in the outer myometrium of adenomyosis patients may differ from that in the inner myometrium and, more specifically, may be related to the presence of pelvic endometriosis [84].

While still controversial, the association between external adenomyosis and DENs has been repeatedly demonstrated, so it cannot be disregarded when studying or treating these diseases. Elucidating the nature of this association may be critical to better classifying these entities and understanding predisposition determinants leading to ectopic endometrial tissue development [85].

Conclusions

Adenomyosis is a benign uterine disease affecting a considerable number of reproductive-age women and causing pelvic pain, abnormal uterine bleeding, and infertility. The key to offering these patients a better quality of life and even effectively curing their disease is unraveling its complicated pathogenesis. The exact pathogenic mechanisms leading to adenomyosis development, progression, and related symptoms still need to be ascertained but remarkable progress has been made over recent years. Two main hypotheses have been proposed to explain the pathogenesis of adenomyosis, but neither has yet been experimentally corroborated. The first and most universally accepted suggests involvement of repeated cycles of TIAR, with subsequent invagination of basal endometrial tissue into the myometrium, while the second contends that adenomyotic lesions are generated de novo via differentiation of embryonic pluripotent Müllerian remnants or adult stem cells in the uterus.

The TIAR/invagination hypothesis remains the most popular and most widely investigated theory, but requires modification to include more recently discovered mechanisms linked to lesion generation and disease progression. At the same time, the hypothesis of de novo development of adenomyotic lesions might explain a small proportion of adenomyosis cases not accounted for by the former theory, including women with Rokitansky-Küster-Hauser syndrome. Both hypotheses have strengths and weaknesses in explaining the different forms and manifestations of adenomyosis. In the end, it could be that a disease that implicates so many molecular mechanisms is simply too complex for one theory to cover all types.

Different mechanisms and their combinations and interactions may explain the enigmatic nature of adenomyosis, but fundamental aspects of disease initiation and progression, need to be further elucidated: What is the exact cause and mechanism behind hyperestrogenism in adenomyosis? What is the trigger converting normal uterine contractility to hypercontractility and inducing trauma to the JZ? Are different forms of adenomyosis actually separate entities with distinct pathogeneses? These are just some of the questions that remain. More research in the field is of paramount importance to find reliable answers to these crucial questions.

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Compliance with Ethical Standards

Conflict of Interest CAS and MMD have no conflict of interest to declare. JD is a member of the SAB of ObsEva and PregLem.

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