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Pathogenesis of uterine adenomyosis: invagination or metaplasia?

Javier García-Solares, M.Sc.,[a] Jacques Donnez, M.D., Ph.D.,[b] Olivier Donnez, M.D., Ph.D.,[c] and Marie-Madeleine Dolmans, M.D., Ph.D.[a,d]

[a] Pôle de Recherche en Gynécologie, Institut de Recherche Expérimentale, Université Catholique de Louvain; and [b] Société de Recherche pour l'Infertilité, Brussels, Belgium; [c] Institut du Sein et de Chirurgie Gynécologique d'Avignon, Polyclinique Urbain V (ELSAN Group), Avignon, France; and [d] Gynecology Department, Cliniques Universitaires Saint Luc, Brussels, Belgium

Adenomyosis is a commonly diagnosed estrogen-dependent gynecological disorder that causes pelvic pain, abnormal uterine bleeding, and infertility. Despite its prevalence and severity of symptoms, its pathogenesis and etiology have not yet been elucidated. The aim of this manuscript is to review the different hypotheses on the origin of adenomyotic lesions and the mechanisms involved in the evolution and progression of the disease. Two main theories have been proposed to explain the origin of adenomyosis. The most common suggests involvement of tissue injury and the repair mechanism and claims that adenomyosis results from invagination of the endometrial basalis into the myometrium. An alternative theory maintains that adenomyotic lesions result from metaplasia of displaced embryonic pluripotent Müllerian remnants or differentiation of adult stem cells. Previous investigations performed in human adenomyotic lesions and corroborated by studies in mice supported the involvement of the epithelial-mesenchymal transition process in the early stages of progression and spread of adenomyosis. However, studies conducted in a recently developed baboon model indicate that collective cell migration may be implicated in the later events of invasion. This suggests that the invasiveness of this complex uterine disorder is not driven by a single mechanism of migration but by a time-dependent combination of two processes. (Fertil Steril® 2018;109:371–9. ©2018 by American Society for Reproductive Medicine.)

Key Words: Tissue injury and repair, stem cells, Müllerian remnants, epithelial-mesenchymal transition, collective cell migration

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Adenomyosis is a commonly encountered benign uterine disease, affecting 19.5% of women of reproductive age (1). Histopathologically, it is characterized by the presence of ectopic endometrial tissue (endometrial glands and/or stroma) in the myometrium, surrounded by hyperplastic and hypertrophic smooth muscle (2, 3). Ectopic endometrial implants are known to follow different distribution patterns in the myometrium, giving rise to two main forms of the disease: focal and diffuse. Adenomyosis is described as focal when a circumscribed nodular collection is identified but considered diffuse when different groups of endometriotic glands and stroma are distributed throughout the myometrium (4, 5). Alternatively, in some rare cases adenomyosis may also present as a large cyst (cystic adenomyoma) (5, 6).

The clinical presentation of adenomyosis includes pelvic pain, abnormal uterine bleeding, and infertility (7–10), but its symptomatology is not specific and may overlap with other gynecological diseases like endometriosis and leiomyomas, thus hampering preoperative diagnosis (11, 12). Imaging techniques, such as transvaginal ultrasound and magnetic resonance imaging, have led to major advances, allowing new conservative treatments to be developed for adenomyosis (13–16). However, the gold standard for its diagnosis is still histological examination after surgery, which will be elaborated upon by Gordts et al. (12) and Bazot et al. (16)

Endometriosis and adenomyosis are closely linked diseases (6, 17, 18), their rate of coexistence varying according to the endometriosis phenotype involved, as recently demonstrated by Chapron et al. and Leyendecker et al.(6, 17, 18). They also share a number of features in terms of

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Reprint requests: Professor Marie-Madeleine Dolmans, M.D., Ph.D., Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Avenue Mounier 52, bte B1.52.02, B-1200 Brussels, Belgium (E-mail: marie-madeleine.dolmans@uclouvain.be).

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symptomatology, histology, and molecular alterations (19–21). Nevertheless, there are several differences in their pathogenesis and pathogenic mediators (22).

Despite its prevalence and the severity of symptoms, little is known about the pathogenesis and etiology of adenomyosis. The present manuscript therefore sets out to review the different pathogenic theories on adenomyosis, as well as available animal models to study the disease.

HYPOTHESIS ON THE ORIGIN OF ADENOMYOSIS

Although the pathogenesis and etiology of adenomyosis remain unkown, two main theories have been proposed in the literature: invagination of the endometrial basalis as a result of activation of the tissue injury and repair (TIAR) mechanism and metaplasia of displaced embryonic pluripotent Müllerian remnants or differentiation of adult stem cells.

Invagination of the Endometrial Basalis: Hyperestrogenism, Hyperperistalsis, and TIAR Mechanism Activation

Steroid hormones play a central role in the etiology of adenomyosis. Indeed, supraphysiological estrogen production (hyperestrogenism) due to local paracrine activity in the eutopic and ectopic endometrium of patients with adenomyosis may be a preliminary status, contributing to the origin of the disease. This concept is supported by the elevated levels of E_2 often observed in the menstrual blood of women with adenomyosis compared with peripheral blood levels (23).

Gene polymorphisms causing increased production (aromatase cytochrome P450-1B1 [CYP1B1] 432 C/G and cyclooxygenase-2 [COX-2] 1195 G/A) and decreased metabolism (catechol-O-methyltransferase [COMT] 158 G/A) of estrogens are associated with a higher risk of adenomyosis development (24, 25). For this reason, hyperestrogenism is suggested to result from increased local aromatization and decreased local estrogen metabolism in the eutopic and ectopic endometrium of patients with adenomyosis. Indeed, as shown by Kitawaki et al., aromatase cytochrome P450, a heme-containing enzyme that catalyzes reactions involved in steroidogenesis, is not present in the endometrium of disease-free uteri. It is, however, found in the eutopic endometrium of patients with adenomyosis, promoting estrogen biosynthesis and higher estrogenic bioavailability due to local aromatization of circulating androgens (T) into E_2 (26). Reduced conversion of E_2 to the less potent estrone was also observed in the eutopic and ectopic endometrium of patients with adenomyosis, as a consequence of decreased expression of 17-β hydroxysteroid dehydrogenase type 2 (17-β HSD2) enzyme (27).

P typically counteracts estrogen-promoted proliferation in healthy endometrium, but not in patients with adenomyosis. In these subjects, stromal cells of the endometrial functionalis and basalis show lower immunoreactivity for isoform B of the P receptor (PR-B) in eutopic endometrium compared with disease-free endometrium, leading to loss of its action and finally a mechanism of P resistance (28, 29). Hence, during the secretory phase of the cycle, estrogen-driven proliferative effects on the endometrium are not adequately harnessed by P, fostering abnormal endometrial proliferation. Moreover, in adenomyosis, hyperestrogenism may promote elevated oxytocin-mediated uterine activity, resulting in increased mechanical strains and stresses that could injure cells in the junctional zone (JZ) close to the fundocornual raphe (17,30–32). Altered endometrial proliferation and hyperperistalsis-induced tissue microtrauma in the JZ due to supraphysiological estrogen production may therefore enhance endometrial intramyometrial invagination (Figs. 1A and 2A).

Indeed, as evidence of tissue microtrauma, levels of anti-smooth muscle antibody–positive and collagen I–positive myofibroblasts are significantly higher in the JZ of women with adenomyosis than in those without (33).

The TIAR mechanism is then activated in response to tissue autotraumatization (17, 30, 31). This mechanism leads to a specific physiological process that promotes local production of interleukin-1 and induces activation of COX-2, causing production of prostaglandin E_2. Steroidogenic acute regulatory protein and P450 aromatase are subsequently activated, allowing T formation and aromatization to E_2 and contributing to the hyperestrogenic status of the eutopic endometrium. E_2 exerts its proliferative and healing effects by means of estrogen receptors (ERs, ER-β in this case). However, in normal healing, increased production of estrogens ceases, but in the uterus, they stimulate oxytocin-mediated hyperperistalsis through ER-α, which inhibits the healing process (Fig. 1B). Thus, a positive feedback mechanism is generated, by which chronic hyperperistalsis in the JZ promotes repeated cycles of autotraumatization, leading to constant disruption of the muscular fibers in the myometrial wall. This worsens with each cycle and consequently increases invagination of the endometrial basal layer into the myometrium, eventually leading to establishment of adenomyotic lesions (Figs. 1A, 1B, and 2A). Moreover, as expression of matrix metalloproteinases (MMPs) -2 and -9 was found to be significantly higher in the eutopic endometrium of adenomyotic lesions than in the endometrium of disease-free women (34), it is possible that these proteases may also be involved in the intramyometrial endometrial invagination process. In addition, because they may present with tissue damage to the endometrial-myometrial interface, cesarean delivery, increased birth rates, and prior uterine surgery were revealed by a number of retrospective studies to be risk factors for adenomyosis (35–38), reinforcing the key importance of tissue microtrauma in the development of this disease.

De Novo Development from Metaplasia of Displaced Embryonic Pluripotent Müllerian Remnants or Differentiation of Adult Stem Cells?

Although a number of human and experimental studies favor the hypothesis of endomyometrial invagination, in our present understanding of adenomyosis etiology, an alternative theory proposes that adenomyotic lesions may originate de novo from metaplasia of displaced embryonic pluripotent

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