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Review article

Epithelial-to-mesenchymal transition in the development of adenomyosis

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ABSTRACT

Adenomyosis is a hormone-related disease that affects 10–66% of women, and women with this disorder suffer from menorrhagia, dysmenorrhea, pelvic pain, abnormal uterine bleeding, and/or infertility. Regarding the etiology of the disease, the current trend of thought is that adenomyosis or adenomyoma results as a down-growth and invagination of the endometrial basalis into the adjacent myometrium after disruption of the normally intact boundary between the two. The eutopic endometrium of adenomyosis presents invasive characteristics, including increased angiogenesis and proliferation, decreased apoptosis, induction of the local production of estrogens, induction of progesterone resistance, and impaired cytokine expression, and these changes enhance the ability of the endometrium to infiltrate the junctional zone myometrium and the growth of ectopic tissue. Hysterectomy is the major strategy to relieve secondary dysmenorrhea caused by adenomyosis. However, fertility and uterine preservation are compromised by such treatment. The traditional pharmacological therapies for adenomyosis are primarily aimed at the suppression of endogenous estrogen production, but the results are not satisfactory. Thus, there is an urgent need to develop novel treatment strategies for adenomyosis. There has been evidence that indicates that the estrogen-induced epithelial–mesenchymal transition (EMT) may play a role in the development of adenomyosis. In this article, we will concentrate on the estrogen-induced EMT in the pathogenesis of adenomyosis.

Introduction

Adenomyosis is a common gynecologic disorder that affects 10–66% of women, and women with adenomyosis often present with menorrhagia, dysmenorrhea, pelvic pain, abnormal uterine bleeding, and/or infertility.[1] The disorder is defined as the presence of ectopic endometrial glandular and stromal cells located 2.5 mm below the endometrial-myometrial interface with surrounding myometrial hyperplasia and hypertrophy.[2–4] In the past, the term "adenomyoma" was used to describe this type of lesion. Until 1925, 2 years before Sampson[5] created the term "endometriosis" to represent the presence of uterine mucosa in the peritoneal cavity, Frankl[6] used the term "adenomyosis" to describe the direct connection of the endometrium with the islands of mucosa located in the musculature. Frankl[6] defined the term "adenomyosis uteri" and explained that "I have chosen the name of adenomyosis, which does not suggest any inflammatory genesis as do terms like adenometritis, adenomyositis, and adenomyometritis". In 1972, Bird[2] provided the current definition of adenomyosis as "adenomyosis may be defined as the benign invasion of endometrium into the myometrium, producing a diffusely enlarged uterus which microscopically exhibits ectopic non-neoplastic, endometrial glands and stroma surrounded by the hypertrophic and hyperplastic myometrium".[7]

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Hysterectomy is the major strategy to relieve secondary dysmenorrhea caused by adenomyosis. However, fertility and uterine preservation are compromised by such treatment. Removing adenomyotic lesions instead of hysterectomy is another strategy to treat adenomyosis,[8,9] however, the effect is temporary, and most women quickly develop adenomyosis and must undergo hysterectomy within 1 year. Even if a normal pregnancy is achieved after removing adenomyotic lesions, safety remains a major concern during pregnancy. Residual adenomyosis in the myometrium combined with the possible inhibition of pregnancy-related changes, such as uterine softening, may increase the risk of miscarriage or uterine rupture. Traditional pharmacological therapies for adenomyosis are primarily aimed at the suppression of endogenous estrogen production by the application of GnRH agonists and low-dose oral contraceptives.[10] However, the results are not satisfactory. Thus, there is an urgent need to develop novel treatment strategies for adenomyosis.[11]

The pathogenesis of adenomyosis still remains unclear, and there are several postulated mechanisms of pathogenesis: invagination of basal endometrium, local hyperestrogenism, and mechanical forces manifesting as hyper or dysperistalsis.[3,4,12–16] Recently, there have been several studies that proposed that the estrogen-induced epithelial–mesenchymal transition (EMT) may play a role in the development of adenomyosis.[17–19] EMT is a process by which epithelial cells lose their polarity and are converted to a mesenchymal phenotype that is crucial in embryogenesis, fibrosis, and tumor metastasis.[20] In this review, we will concentrate on the pathogenesis of adenomyosis, which is related to EMT.

Pathogenesis of adenomyosis: Invagination of the basal endometrium

The current definition of adenomyosis is the benign invasion of the endometrium into the myometrium, producing a diffusely enlarged uterus, which microscopically exhibits ectopic non-neoplastic, endometrial glands, and stroma surrounded by the hypertrophic and hyperplastic myometrium.[2,7] Brosens et al[21] demonstrated on a magnetic resonance image (MRI) that there were two distinct zones: the submucosal layer, also called the inner myometrium (IM) or junctional zone (JZ), and the outer myometrium (OM). The JZ is not only structurally different but also functionally different from the outer myometrium. The irregular thickening of the JZ has been postulated as the magnetic resonance criterion for the diagnosis of adenomyosis. Brosens et al[21] postulated that this magnetic resonance appearance relies on the disruption of the inner myometrial architecture secondary to smooth muscle hyperplasia. Adenomyosis can also be diagnosed by three-dimensional (3D) ultrasonography, which reveals irregular thickening of the JZ associated with adenomyosis. Disruption of the specific microenvironment in the basal endometrium may also explain the structural and functional abnormalities of the JZ, such as hyperperistalsis, dysperistalsis, and inordinate smooth muscle proliferation associated with endometriosis and adenomyosis.[22–24]

Several human and experimental studies proposed that adenomyosis occurs by invagination of the basal endometrium into the JZ.[25] On imaging, abnormal thickening of the subendometrial myometrium includes basal endometrium and the JZ. The JZ may represent a region of structural weakness and myometrial dysfunction of varying severity susceptible to an invagination of the stromal cells.[25] Following the invagination of stromal cells, invasion of glandular cells, abnormal growth, and differentiation, these cells are subsequently surrounded by hypertrophic and hyperplastic myometrium.[26]

These data suggest that adenomyosis may be caused by defects in the formation of the JZ of the uterus and that invagination of the endometrium may play a role in the pathogenesis of adenomyosis.

Chronic inflammation and angiogenesis in adenomyosis

Chronic inflammation plays a crucial role in the pathogenesis of adenomyosis, as the presence of ectopic lesions is associated with the overproduction of prostaglandins, cytokines, and chemokines.[3,27] Abundant macrophages infiltrating the ectopic lesion express typical manifestations of facilitating growth and promoting neuroangiogenesis. In the peritoneal fluid of patients with endometriosis, there is a unique protein, ENDO-1, which is similar to haptoglobin that can bind to the macrophages and reduce their phagocytic ability. Furthermore, after binding to ENDO-1, the macrophages produce more interleukin-6 (IL-6).[28] Other increased cytokines include macrophage migration inhibitory factor (MIF), tumor necrosis factor-α (TNF-α), IL-1β, IL-8, regulated on activation normal T expressed and secreted (RANTES), and monocyte chemotactic protein-1 (MCP-1). Among these cytokines, IL-8, RANTES, and MCP-1 also act as chemoattractants, which facilitate the recruitment of macrophages and cause subsequent abundant peritoneal cytokine accumulation (Fig. 1)[3,27,29]

Aberrant prostaglandin accumulation also plays a role in the disease pathogenesis as well as in the clinical manifestations of dysmenorrhea, chronic pelvic pain, and infertility. Peritoneal macrophages from women with endometriosis express higher levels of cyclo-oxygenase-2 (COX-2) and release significantly higher amounts of prostaglandins than macrophages from healthy women.[30] In the microenvironment at the ectopic lesions, TNF-α promotes endometrial cell production of prostaglandin F2α (PGF2α) and PGE2.[31] The IL-1β activation of COX-2 increases production of PGE2, which subsequently activates steroidogenic acute regulatory protein (StAR) and aromatase. Therefore, estrogen completes a positive feedback loop that induces the local hyperestrogenism by upregulating PGE2 synthesis. This pathway highlights the interplay of estrogen dependence and inflammation in the disease pathogenesis.[32,33] Moreover, the macrophage nuclear factor-kappa B (NF-κB)-dependent pathway is also involved in the pathogenesis and induces the subsequent transactivation of controlling angiogenesis and tissue remodeling.[34,35]

Increased invasiveness

Adenomyosis can be diagnosed by imaging studies with MRI and 3D ultrasonography, on which there is irregular thickening of the JZ and the so-called inner myometrium that is associated with adenomyosis.[22,23] Several human and experimental studies proposed that adenomyosis occurs by invagination of the basal endometrium into the inner layer of the IM known as the JZ.[25] On imaging, abnormal thickening of the subendometrial myometrium includes the basal endometrium and the JZ. The JZ may represent a region of structural weakness and myometrial dysfunction of varying severity that is susceptible to an invagination of the stromal cells.[25] Following invagination of the stromal cells, invasion of glandular cells, abnormal growth, and differentiation, these cells are subsequently surrounded by hypertrophic and hyperplastic myometrium.[26] These findings from imaging studies suggest that adenomyosis may be caused by defects in the formation of the JZ of the uterus.

Moreover, the increased invasiveness of the endometriotic cells lends weight to the basal endometrium invagination hypothesis.[36] The nonmalignant invasive endometriotic cells were identified as lacking the tumor suppressor molecule, E-cadherin, in contrast to the eutopic endometrium.[37] Benagiano and Brosens[38] suggested that the eutopic endometrium of adenomyosis presented more