RBM ONLINE

ELSEVIER

Review

Pathogenesis of adenomyosis: an update on molecular mechanisms

Silvia Vannuccini [a], Claudia Tosti [a], Francisco Carmona [b], S Joseph Huang [c,d], Charles Chapron [e,f,g], Sun-Wei Guo [h,i], Felice Petraglia [a,*]

[a] *Obstetrics and Gynecology, Department of Molecular and Developmental Medicine University of Siena, Siena, Italy*
[b] *Clinical Institute of Gynecology, Obstetrics, and Neonatology, Hospital Clinic, Universitat de Barcelona, Barcelona, Spain Group of Endocrinology, Gynecology and Human Reproduction, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain*
[c] *Department of Obstetrics and Gynecology, E-Da Hospital, I-Shou University, Kaohsiung, Taiwan*
[d] *Department of Obstetrics and Gynecology, Morsasni College of Medicine, University of South Florida, Tampa, FL, USA*
[e] *Université Paris Descartes, Sorbonne Paris Cité, Faculté de Médecine, Assistance Publique-Hôpitaux de Paris, Hôpital Universitaire Paris Centre, Centre Hospitalier Universitaire Cochin, Department of Gynaecology Obstetrics II and Reproductive Medicine, Paris, France*
[f] *Institut Cochin, INSERM U1016, Laboratoire d'Immunologie, Université Paris Descartes, Sorbonne Paris Cité, Paris, France*
[g] *Département de Génetique, Développement et Cancer, Université Paris Descartes, Sorbonne Paris Cité, Paris, France*
[h] *Shanghai OB/GYN Hospital, Fudan University, Shanghai 200011, China*
[i] *Shanghai Key Laboratory of Female Reproductive Endocrine-Related Diseases, Fudan University, Shanghai, China*

Felice Petraglia is Professor and Chairman of Obstetrics and Gynecology. He is Fellow ad Eundem of the Royal College of Obstetricians and Gynecologists (RCOG). He was President of the Society for Gynecologic Investigation (SGI). He is Editor-in-Chief of *Human Reproduction Update* and Section Head in Reproductive Endocrinology of Faculty 1000 Medicine.

KEY MESSAGE

Sex steroid receptors, proliferation and fibrosis, inflammatory mediators and neuroangiogenesis are key pathogenetic mediators of adenomyosis-related pain, abnormal uterine bleeding and infertility.

A B S T R A C T

Adenomyosis is a uterine disorder becoming more commonly diagnosed in women of reproductive age because of diagnostic imaging advancements. The new epidemiological scenario and the clinical evidence of pelvic pain, abnormal uterine bleeding and infertility are changing the classic perspective of adenomyosis as a premenopausal disease. In the last decade, the evaluation of multiple molecular mediators has improved our knowledge of pathogenic mechanisms of adenomyosis, supporting that this is an independent disease from endometriosis. Although they share common genetic mutations and epigenetic changes in sex steroid hormone receptors and similar inflammatory mediators, an increasing number of recent studies have shown pathogenic pathways specific for adenomyosis. A PubMed search up to October 2016 summarizes the key mediators of pain, abnormal uterine bleeding and infertility in adenomyosis, including sex steroid hormone receptors, inflammatory molecules, extracellular matrix enzymes, growth factors and neuroangiogenic factors.

* Corresponding author.
E-mail address: felice.petraglia@unisi.it (F Petraglia).

http://dx.doi.org/10.1016/j.rbmo.2017.06.016
1472-6483/© 2017 Published by Elsevier Ltd on behalf of Reproductive Healthcare Ltd.

Please cite this article in press as: Silvia Vannuccini, et al., Pathogenesis of adenomyosis: an update on molecular mechanisms, Reproductive BioMedicine Online (2017), doi: 10.1016/j.rbmo.2017.06.016

Introduction

Adenomyosis is defined as the presence of ectopic endometrial glands and stroma surrounded by hyperplastic smooth muscle within the myometrium. It is a uterine disorder clinically presented with pelvic pain, abnormal uterine bleeding (AUB) and infertility. Dysmenorrhoea and dyspareunia are the most common symptoms; however, the clinical presentation of adenomyosis is often mixed and occasionally it may even be asymptomatic (Farquhar and Brosens, 2006). Rokitansky first recognized adenomyosis in 1860 but the term was first used by Frankl in 1925 (Benagiano et al., 2012; Leyendecker et al., 2006). Before the advancement of imaging techniques such as transvaginal ultrasound scan (TVUS) and magnetic resonance imaging (MRI), adenomyosis could only be diagnosed by histology after hysterectomy. Two different pathological aspects of adenomyosis are described: diffuse and focal forms (when a defined nodule is found, the term adenomyoma is also used). Adenomyosis and endometriosis share a number of features and it was found that, at least in some subgroups, the two conditions often coexist (Lazzeri et al., 2014; Li et al., 2014), so much so that for a long time adenomyosis had been termed endometriosis *interna*. Nevertheless, they are considered as two distinct entities because many differences have been observed in pathogenesis, risk factors and clinical presentation (Benagiano et al., 2014). Despite all these differences, the two conditions have many similarities in definition, symptomology and molecular aberrations (Li et al., 2013). Above all, adenomyosis and endometriosis share the same commonality of experiencing cyclic bleeding (Liu et al., 2016; Shen et al., 2016).

The pathogenic mechanisms of adenomyosis development are still debatable; however, sex steroid hormone aberrations, inflammation, altered cell proliferation and neuroangiogenesis are likely key pathogenic mechanisms of pain, AUB and infertility in adenomyosis. In this review, we summarize all the available evidence on specific pathways and mediators involved in the pathogenesis of adenomyosis, explaining the clinical presentation of the disease.

Sources

A PubMed search of the literature from 1950 to October 2016 was performed in order to summarize all evidence on pathogenic mechanisms of adenomyosis development and clinical presentation. All pertinent articles were examined and their reference lists were reviewed in order to identify other studies for potential inclusion. The literature search included the following terms: 'adenomyosis', 'adenomyoma', 'pathogenesis', 'pain', 'abnormal uterine bleeding', 'infertility', 'sex steroid hormones', 'sex steroid hormone receptors', 'inflammation', 'neoangiogenesis', 'growth factors', 'extracellular matrix (ECM)', 'fibrosis', 'proliferation' and 'neurogenic factors'. Only peer-reviewed, English-language journal articles were included.

Pathogenic hypotheses

Despite the prevalence of the disease, its precise aetiology and physiopathology remain in part unknown. Some hypotheses have been developed, suggesting the role played by the endometrium, the mechanism of tissue injury and repair (TIAR) and stem cell theory.

Invasion from the endometrium

According to the current theory, adenomyosis develops through downgrowth and invagination of the endometrium *basalis* into the myometrium through an altered or absent junctional zone (JZ) (Bergeron et al., 2006; Parrott et al., 2001). Thus, the endometrium can slip through bundles of weak smooth muscle fibres that have loosened their tissue cohesion. Dysregulation of genes and pathways in the eutopic endometrium may predispose to ectopic migration and implantation. The analysis of the global transcriptome of eutopic endometrial cells from women with clinically significant adenomyosis revealed 140 up-regulated and 884 down-regulated genes, compared with controls. Genes involved in regulation of apoptosis, steroid hormone responsiveness and extracellular matrix remodelling as well as microRNAs of unknown significance were found to be highly differentially expressed. Affected canonical pathways included eukaryotic initiation factor 2 (eIF2) signalling, oxidative phosphorylation, mitochondrial dysfunction, oestrogen receptor (ER) signalling, and mammalian target of rapamycin (mTOR) signalling (Herndon et al., 2016). These aberrant pathways may predispose toward the development, migration and survival of ectopic endometrial implants beyond the myometrial interface. However, further studies are needed to elucidate the biological significance of these aberrations, especially in the early developmental stage of the disease.

Mechanism of TIAR

The phenomenon of endometrial invasion may happen in a predisposed myometrium or in a traumatized endometrial–myometrial interface (Benagiano et al., 2012). Uterine auto-traumatization and initiation of the mechanism of TIAR have been considered as the primary events in the disease process. A condition of chronic proliferation and inflammation induced at the level of the archimetra by chronic uterine auto-traumatization supports one of the theories for adenomyosis pathophysiology (Leyendecker et al., 2015). Accordingly, the TIAR mechanism, in response to increased intrauterine pressure, may promote the migration of fragments of basal endometrium into the myometrium. In a recent study a new software was used to develop a conceptual two-dimensional model of the uterine wall subjected to a variety of intrauterine sinusoidal pressure waves with varying frequencies. It was noted that a decrease in wavelength and an increase in frequency of the subjected pressure wave led to high levels of stress near the inner uterine cavity. During menstruation, the highest stress was observed at the endometrial–myometrial interface. Hence, high stress caused by increased uterine activity may lead to tissue lesions and detachment of endometrial cells (Shaked et al., 2015).

Chronic peristaltic myometrial contractions induce microtrauma to the JZ, causing a vicious cycle in which local oestrogen production, COX-2 mediated (Chen et al., 2010a), promotes uterine peristalsis and further auto-traumatization (Gargett et al., 2016; Leyendecker et al., 2009).

On the basis of small-diameter nerve fibre proliferation observed in the myometrium of patients with chronic pelvic pain (Quinn and Kirk, 2002), Quinn postulated that nerve injury (denervation) in the uterus and/or uterosacral ligaments may lead to endometriosis (Quinn, 2004; Quinn and Kirk, 2004; Quinn, 2011) and also to adenomyosis (Quinn, 2007). Nerve injury might be due to either difficult intrapartum episodes or persistent straining to achieve defecation. The resulting re-innervation of the uterine isthmus may be the primary source of many pain symptoms in adenomyosis (Quinn, 2007).

While these hypotheses and theories are intuitive and attractive, the biggest challenge is to make them falsifiable, i.e. able to be tested with a well-designed experiment. In addition, these hypotheses and

Please cite this article in press as: Silvia Vannuccini, et al., Pathogenesis of adenomyosis: an update on molecular mechanisms, Reproductive BioMedicine Online (2017), doi: 10.1016/j.rbmo.2017.06.016