



Medicine in focus

New evidence in endometriosis

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ABSTRACT

Endometriosis is a recurrent and benign gynecological disorder characterized by the presence of endometrial tissue outside the cavity of the uterus. It is one of the most common diseases in the gynecological field, affecting about 10% of the female population in reproductive age. Despite this, its pathogenesis is still unacknowledged, there is a lack of early diagnostic markers and current therapies are only symptomatic. Considering the relevant health problems caused by endometriosis, all new information on this disease may have important clinical implications. The aim of this article is to summarize the latest advances in the pathogenesis, diagnosis and therapy of endometriosis that have recently been proposed by our research group. The possible clinical implications of these findings will be discussed.

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1. Introduction

Endometriosis is defined as the growth of the endometrial glands and stroma at extra-uterine sites, which are most commonly implanted over and under visceral and peritoneal surfaces within the female pelvis but which can also be found in the connective tissue in the pelvis areas and, more rarely, in any anatomic district (Baldi et al., 2008; Bulun, 2009; Giudice and Kao, 2004). It is a prevalent gynecological disorder, its frequency being 20–50% in women with fertility problems (Signorile et al., 2009a). Endometriosis causes a clinical syndrome that includes progressive ovarian failure, infertility, and precocious menopause, and is associated with specific symptoms such as headache, chronic heavy pelvic pain, dysmenorrhea, and dyspareunia. It is responsible for more than 100,000 hysterectomies each year in the United States alone, with a significant annual health cost (Missmer et al., 2004). Endometriosis, therefore, has an important socio-economic impact, because it greatly lowers the quality of life in a significant portion of the population and is responsible for significant health expenditure, both in terms of its diagnosis and treatment and the loss of economic performance of the patients. Nevertheless, there are no sufficiently sensitive and specific signs and symptoms nor

diagnostic tests that allow an early clinical diagnosis of endometriosis (Ballard et al., 2006), and the currently accepted treatments are invasive or only symptomatic with the consequence that often such therapeutic strategies are associated with recurrence and unwanted side-effects. The aim of this article is to summarize the recent results produced by our research group on endometriosis, concerning the clarification of the pathogenic mechanisms responsible for the onset of this disease, the identification of potential markers for early diagnosis and for the topographic localization of the endometriosis spots *in vivo*, and the recognition of possible therapeutic targets.

2. Pathogenesis

Many theories have been proposed to explain the onset and development of endometriosis. The retrograde menstruation/transplantation theory, proposed in the 1920s by Sampson, is still the most widely accepted explanation for the pathogenesis of endometriosis (Sampson, 1927). In the last few years, scientists have proposed some different modalities for its pathogenesis, coelomic metaplasia (Nisolle and Donnez, 1997) and endometrial stem cells (Benagiano et al., 2014) being the most well recognized hypotheses. Nevertheless, this proposed theories remain just hypotheses without a straight scientific demonstration of their validity.

Recently, our research group has demonstrated the presence of an ectopic endometrium with a molecular phenotype identical to that of the eutopic endometrium in a significant number

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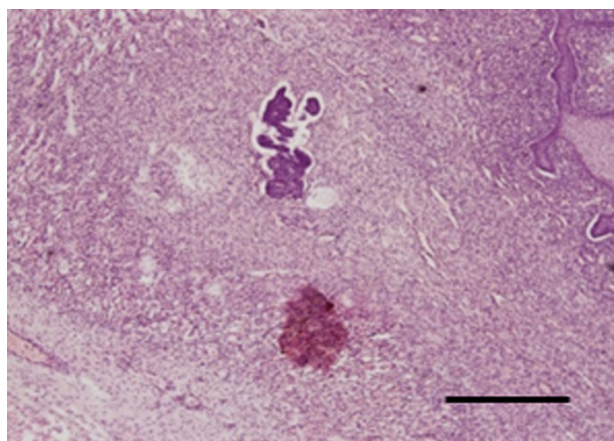


Fig. 1. Histological appearance of an endometriotic gland found in the recto-vaginal septum of a female fetus (in the left side the epithelium of the vagina is visible). Scale bar = 100 μ m.

of human female fetuses analyzed by autopsy (Signorile et al., 2009b; Signorile and Baldi, 2010). In Fig. 1 a typical fetal endometriosis gland is depicted. We have suggested that molecular events during a critical window of time in the embryo could be responsible for perturbations of the fine-tuning mechanisms responsible for the correct development of the female genital system. This, in turn, would allow the dislocation of endometrial tissue outside the uterine cavity during the earlier steps of organogenesis. The onset and progression of this phenomenon may result from disruptions by genetic and/or epigenetic factors of some organizational events associated with the development of the embryonic uterine wall. This theory is also supported by the increase in the incidence of endometriosis in patients affected by uterine malformations (Signorile et al., 2010). In a recent work we have described an endometriosis-like phenotype in mice exposed *in utero* to the endocrine disruptor bisphenol (Signorile et al., 2010). Indeed, strong epidemiological data link the *in utero* exposure to an endocrine disruptor and the insurgence of endometriosis later in adult life (Missmer et al., 2004). Finally, we have been able to demonstrate, by using a genomic approach for the comparison of the transcriptional profiling of the ectopic endometrium with the corresponding eutopic one, that several genes involved in embryogenesis are differentially expressed in the endometriosis tissues and that this expression pattern is independent of the menstrual and hormonal phase (Crispi et al., 2013). Among the genes differentially expressed, we found: (a) LEFTY2, BMP2 and BMP4, three members of the transforming growth factor-beta super-family that include growth and differentiation proteins; (b) GREM1 and FST (Follistatin), that are BMP antagonists; (c) SERPINE1 and SERPINE2, members of the serine protease inhibitor (SERPIN) family that are involved in tissue remodeling.

These last remarks further sustain the hypothesis that endometriosis might be generated by a remodeling in gene expression during embryogenesis. These observations may lead us to reconsider the pathogenesis of endometriosis and to dramatically change our approach to the disease.

3. Diagnosis

Endometriosis is one of the diseases where the time interval between the onset of the symptoms and the diagnosis is unacceptably long and the definitive diagnosis can only be achieved by invasive surgical procedures (Giudice and Kao, 2004). Nevertheless, this is true for endometriotic lesions on the surface of the abdominal organs and for the foci clinically evident, while

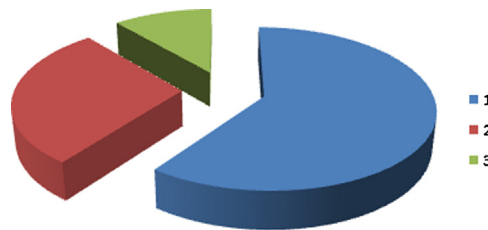


Fig. 2. Histogram showing the significant higher sensitivity values achieved by Zn-alpha2-glycoprotein (blue slice), respect to CA125 (red slice) and CA19.9 (green slice) in diagnosing endometriosis. (For interpretation of the references to color in figure legend, the reader is referred to the web version of the article.)

the deep lesions in the sub-peritoneal areas can be misdiagnosed even when using invasive procedures (Baldi et al., 2008). To date, none of the non-invasive approaches, from blood tests to imaging analyses, have allowed a definitive diagnosis of endometriosis (Bulun, 2009). Despite the fact that several works have tried to define reliable peripheral biomarkers for the diagnosis of endometriosis, there are still no trustworthy blood tests that can be used in routine clinical care (Bulun, 2009). It is evident that a non-invasive diagnostic test for endometriosis would be of great value in clinical practice, especially because it would allow a dramatic reduction in the time currently necessary for the correct identification of endometriosis patients. Our research group, by means of a proteomic approach, has recently defined a small number of proteins differentially expressed in a cohort of endometriosis patients in comparison to a group of healthy women (Signorile and Baldi, 2014a). Interestingly, ELISA assay testing on a different cohort of patients has confirmed the differential expression of at least one of these proteins, Zn-alpha2-glycoprotein, and ROC analysis of these data has demonstrated the statistical significance of this differential expression. Moreover, the sensitivity of this test in diagnosing endometriosis patients was significantly higher compared to the sensitivity of CA125 and CA19.9, the only peripheral blood markers currently used in the clinical setting for the diagnosis of endometriosis (Fig. 2). Therefore, if confirmed on larger groups of patients, these data clearly indicate Zn-alpha2-glycoprotein as a reliable biomarker for the diagnosis of endometriosis. Interestingly enough, this same glycoprotein has recently been proposed as a peripheral diagnostic marker for different cancers, such as breast, prostate and liver carcinomas (Huang et al., 2012).

4. Imaging diagnosis

As we have already stated, the diagnosis of endometriosis can be performed only when endometriosis lesions are observed by laparoscopy and after the histological confirmation of the surgically resected lesions (Baldi et al., 2008). However, it is well established that imaging analyses can be used in the differential diagnosis process and, in several cases, allow at least a presumptive diagnosis, even if they are not able to indicate the exact localization *in vivo* of the endometriosis lesions, especially those with a very small size (Bulun, 2009). Unfortunately, imaging analyses such as magnetic resonance (MR) are not completely effective in the diagnosis of the disease, when present in the sub-peritoneal stromal connective tissue or when the foci are under two or three millimeters; moreover, it is very difficult to diagnose the manifestation of adenomyosis in the early phase of development. Considering the fact that the disease is always multicentric and often microscopic, the possibility of having a detection procedure able to obtain a precise localization of the disease's different loci *in vivo* would ensure the success of the surgical procedure, significantly reducing the occurrence of relapses. MR has displayed a high sensitivity, specificity and accuracy in the identification of the locations and extension

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