Review

Endometriosis-Search for Biomarkers

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Abstract: Numerous studies are seeking noninvasive methods to diagnose endometriosis, but a clinically applicable test is still missing. Current paper compares the current results in our search for the best diagnostic marker. We summarize that despite the extensive research on endometriosis biomarkers, timely diagnosis using specific biomarkers remains an unfilled dream.

Keywords: Biomarkers, Endometriosis, CA125, microRNA

Introduction

Endometriosis is manifested by the presence of both endometrial glandular and stromal cells outside the uterine cavity, mainly in the pelvis. Endometriosis, occurring in 10-20% of females of reproductive age, is characterized by ectopic implantation of endometrial cells with elevated proliferation and migration and represents the leading cause of morbidity among premenopausal women. It is a common, benign and chronic disease affecting 2-18% of women in reproductive age and over 40% of patients with infertility (Missmer and Cramer, 2003). The complex pathogenesis of this enigmatic disorder remains controversial despite extensive research (Baldi *et al.*, 2008). Among existing theories on the cell origin of endometriosis, one should mention retrograde menstruation and implantation, coelomic metaplasia (Burney *et al.*, 2007), embryonic cell rest theory or stem cell theory (Kralickova and Vetvicka, 2015).

Research in the field of endometriosis is limited due to the absence of a low-cost and reliable method for diagnosing endometriosis, especially in the early stages. The validation of numerous markers suggested to be important in endometriosis could represent significant improvement leading to early and non-invasive diagnosis of this disease. So far, the diagnosis is generally achieved by invasive procedures including laparoscopy followed by histology.

Endometrium represents a highly dynamic tissue, with a significant number of molecules relevant to adhesion, attachment, proliferation, invasion and migration (Sundqvist *et al.*, 2012). Numerous studies are seeking noninvasive methods to diagnose endometriosis, but a clinically applicable test is still missing. Most of these studies are focused on finding a single marker which would be up-or down-regulated in patients with endometriosis.

Endometriosis is an estrogen-dependent disease; therefore the presence of estrogen androgen and progesterone receptors is not surprising. However, despite the fact that these steroid receptors play an important role in development of endometriosis, their expression is not specific for diagnostic purposes. A simple, preferably blood, test for endometriosis-specific biomarker/s would offer fast and accurate diagnosis, allowing faster and earlier medical intervention.

Tumor Markers CA125 and CA19-9

Tumor marker CA125 is one of the most studied biomarkers, with more than a 40 year history and over 2,000 published papers (Bast *et al.*, 1998). It is a high MW glycoprotein originally used as a tumor marker for ovarian tumors (Bast *et al.*, 1981). Its use in endometriosis is based on a well-established connection between endometriosis and ovarian cancer (Kralickova *et al.*, 2014). However, it is important to remember that it cannot be used for differential diagnosis between endometriosis and cancer, as the level is increased in patients with both endometriosis and cancer (Lenhard *et al.*, 2009).

It was shown that its level is suppressed during treatment, but elevated again after treatment even in women in whom the disease had not recurred (Vard *et al.*, 1991). In addition to levels in serum, CA125 is also produced *in vitro* by endometrial tissue in explant cultures (Bersinger *et al.*, 1993).

The degree to which the level of serum CA125 is raised in endometriosis correlates with the disease severity (Pittaway and Fayez, 1986), however, the biological significance is still not fully established. Studies comparing levels of CA135, CA19-9 and Ki-67 in late stages of endometriosis found no correlation between serum levels of CA125 and CA19-9 and no strong correlation between serum levels and histochemical staining. With the strong positive correlation between serum CA125 levels and KI-67 labeling index, the authors concluded that serum CA125 might correlate with proliferative activity of endometriotic epithelial cells (Toki *et al.*, 2000). Similarly, the usefulness of CA125 can be increased by simultaneous evaluation of the level of CA72-4 antigen (Anastasi *et al.*, 2013a). Additional findings not only supported this conclusion, but added human epididymis protein 4 as the best approach to confirm the benign nature of endometrioma in women with high level of CA125 (Anastasi *et al.*, 2013b).

The importance of the CA125 biomarker was further supported in a study using 164 women, indicating both CA125 and CA19-9 markers were significantly increased. Further analysis revealed correlation with hsCRP and with the severity of endometriosis (Komur *et al.*, 2015). All these markers were thus suggested to be used in the diagnosis of endometriosis. In addition, both markers are useful in differentiating between endometriosis and ovarian tumors (Nakagawa *et al.*, 2015).

A meta-analysis of the diagnostic value of serum CA125, CA19-9 and CA15-3 used papers published between 2000 and 2014 and concluded that both CA125 and CA19-9 are useful markers for the noninvasive diagnosis of endometriosis, CA1503 is not worth further studies (Shen *et al.*, 2015). Similarly, the known usefulness of the combination of CA-125 and CA19-9 was further improved by testing of IL-6 and hsCRP, particularly during the secretory phase (Sutcu *et al.*, 2015). Many researchers are, however, still convinced that sensitivity and specificity of such markers is insufficiently low (Mol *et al.*, 1998).

MicroRNA

Currently, microRNAs represent novel biomarkers for both endometriosis and endometriosis-related ovarian cancers. MicroRNAs (miRNAs) are a class of short, single-stranded non coding RNA molecules. Latest studies suggested that mRNAs might play an important role in both the development and prognosis of endometriosis. This hypothesis is further strengthened by the fact that mRNAs are exceptionally stable and can be reliably detected in serum.

Using a reverse transcriptase quantitative PCR, Suryawanshi's group identified 23 microRNAs which are differentially expressed in healthy people and patients with endometriosis. These microRNAs were subsequently further evaluated in a larger cohort. The results showed that plasma microRNA expressing patterns might serve as specific and reliable diagnostic biomarkers (Suryawanshi *et al.*, 2013) resulting in some authors suggesting than microRNA studies will lead to changes in current treatment of both endometriosis and ovarian cancer (Neto *et al.*, 2014).

A meta-analysis of 194 studies showed that mRNAs appear to be potent regulators of gene expression in endometriosis (Wei *et al.*, 2015). Based on these studies, the authors proposed the use of mRNAs as both biomarkers and therapeutic agents. The problem with mRNA originated from the fact that there are simply too many of those, the studies found 134 different mRNAs with only 28 of them reported in at least two studies. Another review painted a similarly pessimistic picture (Nothnick *et al.*, 2015).

Genetic Studies

Several genes have been found to be upregulated or changed in endometriosis (Fassbender *et al.*, 2015). The major genes include hypermethylated HOXA10 (Wu *et al.*, 2005) and PR-B (Wu *et al.*, 2006), aromatase (Izawa *et al.*, 2008) and E-cadherin (Wu *et al.*, 2007). However, it is not known if these aberrations are cause or consequence of endometriosis and it seems that the levels are not sensitive for diagnostic purposes. Overexpression of p53 in atypical endometriosis is quite common, but these findings are probably more suited for identification of endometriosis with premalignant potential than for diagnosis of endometriosis "only" (de la Cuesta *et al.*, 2004). Recent whole genome microarray data involving 144 samples from women with endometriosis was performed, but the results are still unclear (Tamaresis *et al.*, 2014).

Immunological Markers

Immunity is one of the proposed factors in pathogenesis of endometriosis, so it is not surprising that inflammatory cytokines and other immunological markers have been suggested (May *et al.*, 2010). Additional potential biomarkers being elevated in endometriosis are TGF-β1, COX-2, VEGF, ER-1α and aromatase (Meng *et al.*, 2011), but their elevated levels are unfortunately not fully endometriosis-specific to be utilized in clinical practice. Despite extensive research,

co consensus exists on the use of cytokines in diagnosis (Fassbender *et al*., 2015).

Human Epididymis Protein 4

Another possible marker is a Human Epididymis protein 4 (HE4), found elevated in endometriosis, particularly in premenopausal women (Ortiz-Munoz *et al*., 2014). Serum concentration can help to differentiate malignant ovarian cancer from ovarian endometriotic cysts (Huhtinen *et al*., 2009). Comparison of both HE4 and CA125 markers favors HE4 over CA125, mainly because even when both markers are increased in non-treated patients, hormone treatment returns concentration of CA125 to normal levels, but concentration of HE4 is significantly below the control levels (McKinnon *et al*., 2015). A multicentric study in four European centers showed that HE4 is a useful biomarker for excluding malignant disease in patients with endometriosis (Zapardiel *et al*., 2016). On the other hand, some studies showed no elevation of HE4 levels in endometriosis (Jacob *et al*., 2010), making the use of this biomarker doubtful. Like with many other markers such as CA125, kallikrein 6 or osteopontin, this marker is probably better suited for diagnostic role in epithelial ovarian cancer (Bandiera *et al*., 2013).

Other Markers

Vitamin E-binding protein afamin is altered in the peritoneal fluid of endometriosis patients. The levels of vitamin E are depressed in these patients, probably due to the lower level of antioxidants. Subsequent study showed correlation between levels of vitamin E and afamin, which was ascribed to increased oxidative stress (Seeber *et al*., 2010a). These findings were, however, less pronounced in patients with stage III and IV disease, making the use of afamin as a biomarker questionable.

Proteomic analysis of serum found six proteins with differential expression between control and endometriotic patients, however, these proteins were able to confirm the diagnosis in only 55% of patients. Combination with other serum markers increased the diagnostic ability to 73% (Seeber *et al*., 2010b).

An interesting study used proteomic fingerprint technology combining nanosized magnetic beads with MALDI-TOF-MS for screening for potential biomarkers in serum. Using 126 patients and 100 healthy volunteers, the study identified three peaks with high separation between endometriosis and control values (Zheng *et al*., 2011). However, this is rather time consuming effort and direct description of peaks found in this study will be necessary for clinical use.

Histochemical analysis showed that epithelial antigen CD10 and Ber-Ep4 expression was positive in most cases of endometrium, in the case of hyperplastic epithelium or cytological atypia, Ber-Ep4 expression was negative (Capobianco *et al*., 2013). As numerous studies suggested the important role of peritoneal fluid, scientists also checked it for possible markers. Levels of galectin-3 positively correlated with the stage of endometriosis and duration of the syndromes, but levels of Stimulation Expressed Gene 2 (ST2) did not (Caserta *et al*., 2014). A more recent study, however, found elevated levels of ST2 in patients with endometriosis and suggested its possible use in correlation with levels of IL-33 (Mbarik *et al*., 2015). However, this study used only Tunisian population, which might influence the outcome.

A promoter of neovasculatization glycodelin A as a biomarker for endometriosis is still questionable. Whereas some studies showed high sensitivity, over 82%, (Kocbek *et al*., 2013), some found no specificity at all (Dropsdzol-Cop and Skrzypulec-Plinta, 2012).

A histochemical analysis focused on expression of matrix metalloproteinases MMP-2 and MMP-9. Using samples from invasive colorectal endometriosis, superficial peritoneal endometriosis and endometrial cancer, the study showed significant differences in expression patterns of these two markers allowing them to be used in evaluation of aggressiveness and invasiveness of endometriosis in different locations (Weigel *et al*., 2012).

One of the currently accepted hypotheses on causes of endometriosis is based on the role of stem cells. Some of the new studies evaluated the expression of stem cells-related markers CD133 and ABCG2. The results suggested that aberrant expression of both these markers in eutopic and ectopic endometrial tissue is associated with the pathogenesis of endometriosis (Liu *et al*., 2015), suggesting that these markers might be utilized in diagnosis. However, more research is clearly needed.

Conclusion

Endometriosis represents a significant medical problem for women in reproductive age. Despite the extensive research on endometriosis biomarkers, timely diagnosis using specific biomarkers remains an unfilled dream. The traditional markers such as CA125 look promising, but never really got into practice. More modern approaches such as use of micro-RNAs suffer from the problem that no endometriotic lesions-specific mRNAs have been identified. So far, biomarker research in this area is still lacking reproducible data. So, the search for the ever-elusive diagnostic biomarker continues.

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Author's Contribution

Both authors equally contributed in this work.

Ethics

The article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues are involved.

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