Nat. Volatiles & Essent. Oils, 2021; 8(4): 1761-1773

IMPROVING THE QUALITY OF DIAGNOSIS OF THE SPREAD OF OVARIAN ENDOMETRIOSIS

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Abstract

The article examines the diagnosis of ovarian endometriosis, which is a chronic, estrogen-dependent, progressive disease. The article deeply discloses the history of the discovery and study of endometriosis; the works of such scientists as Russel W.W., Sampson J.A., Scott R.B., Ranney B., Noble A.D., DmowskiW.P., Gebel H.M., Braun D.P. and others are discussed in the article. It was found that endometriosis is defined as the presence of endometrial glands and stroma-like lesions outside the uterus. The authors noted that endometriosis can undergo malignant transformation; however, it is still not possible to identify intermediate precursors. The authors concluded that the development of reliable biomarkers can provide a positive result in the early detection of endometriosis-associated ovarian cancer. To date, the most promising specific potential biomarker of endometriosis is miRNAs, discovered relatively recently. The search for a biomarker or a set of biomarkers is still open.

KEYWORDS: ovarian endometriosis, malignancy, oncotransforming mechanisms, endometriosis-associated ovarian cancer, biomarkers.

Introduction

Endometriosis is a chronic, estrogen-dependent, progressive disease characterized by the presence of endometrioid tissue, glands and stroma outside the uterine cavity [1]. Estimates of the incidence of endometriosis in the population vary widely. This complex disease, which affects

approximately 10% of women of reproductive age, has profound consequences in the lives of many patients [2]. The ovaries, fallopian tubes and pelvic peritoneum are most commonly affected in endometriosis [3]. Endometriosis is a benign disease, but there is a risk of malignancy, which in some cases justifies radical treatment [4].

Numerous epidemiological studies have shown that nulliparous women and women with short and heavy periods have an increased risk of developing endometriosis. These epidemiological data support the etiological hypothesis of menstrual reflux in the development of endometriosis [5]. Data on the viability of endometrial cells in menstrual discharge and abdominal effusion, successful attempts at experimental implantation of the endometrium in the abdominal cavity, observation of retrograde menstruation in many women who underwent laparoscopy during menstruation, and the relationship between menstrual irregularities and endometriosis make it possible to determine the pathogenetic association in the development of endometriosis [6].

The pathogenesis of this disease is associated with multilocus implantation of endometrium-like cells, accompanied by their increased proliferation, migration, and stimulation of angiogenesis and neurogenesis [7]. The disease most commonly affects women of fertile age and premenopausal women [8]. Understanding of the etiopathogenetic, intrapopulation and molecular genetic aspects of endometriosis is closely related to the history of the discovery and study of endometriosis.

Materials and Methods

Atypical endometriosis is actually the middle stage in the progression from benign to malignant disease [9]. The discovered patterns in the oncotransformation of endometriosis prompted the scientific community to study in detail the features of the malignancy of endometriotic foci and determine the tactics of treatment [10]. The results of these studies have revealed numerous anatomical and physiological features of endometriosis, such as the ability to avoid apoptosis, disrupt the regulation of stem cells, promote neoangiogenesis, metastasis and influence the microenvironment that accompanies the entire pathological process [11,12,13]. The hypothesis that atypical endometriosis may represent a transitional stage between benign endometriosis and cancer originates from histopathological studies. This hypothesis was only a small step towards the assumption that endometriosis is indeed a precancerous condition. This was further confirmed by the fact that more than two thirds of endometriosis-associated ovarian tumors developed in the presence of atypical endometrioid cells in the ovaries. Subsequently, many retrospective studies have recorded a higher incidence of endometriosis in patients with ovarian cancer and vice versa. There are many similarities between ovarian cancer and endometriosis, some of which can influence the incidence. Infertility or late menopause are examples of factors associated with an increased risk. In contrast, hysterectomy, oral contraceptive use, and tubal ligation may reduce the risk.

The ability of endometriosis to undergo malignant transformation is already well established. However, it is still not possible to identify intermediate precursors [14]. The most obvious example is atypical endometriosis with characteristics that are neither benign nor completely malignant. Recent studies have shown that these lesions are present in 50% of endometrioid and clear cell carcinomas

[15].

Recently, it was reported that molecular pathogenetic pathways associated with ARID1A mutations suggest progression from endometriosis to atypical endometriosis and subsequent endometriosis-associated ovarian cancer [16]. Clear cell ovarian adenocarcinoma is a type of chemoresistant cancer often associated with endometriosis [17]. It is assumed that the cause of this malignant disease is the presence of a large amount of free iron in endometrioid cysts, leading to persistent oxidative stress and subsequent carcinogenesis.

Results and Discussion

Endometriosis can be classified into three subtypes based on its histopathology and anatomical location: superficial endometriosis, deep infiltrating endometriosis (DIE), and ovarian endometrioid cysts (known as endometriomas or so-called chocolate cysts) [18]. Superficial endometriosis usually appears on the surface or in the subserous soft tissues of the peritoneum or internal organs. DIE includes lesions that extend into the muscular layer of the intestine, bladder wall, diaphragm, or other organs [19]. Endometrioid ovarian cysts are found in the ovary, usually forming a large cystic structure (clinically interpreted as an adventitious mass) [20].

There is evidence that the CXCL12 / CXCR4 migration axis is involved in the recruitment of BMDSC into endometrial tissue, including ectopic foci. CXCR4 is a chemokine receptor expressed on the surface of stem cells. CXCL12 is the target for CXCR4 [21]. An in vitro study has shown that estradiol increases the expression of CXCL12 and CXCR4 in bone marrow stem cells in mice, while progesterone increases their expression in human endometrial stromal cells. Expression levels of both CXCR4 and CXCL12 are higher in endometriotic foci than in normal uterine endometrium [22]. Culture media from primary cultures of human endometriotic cells induce more BMDSC migration than media from primary cultures of normal endometrium [23].

Studies have shown that during malignancy, CXCL12 / CXCR4 is activated, which in turn increases the expression of metalloproteinase, promotes angiogenesis, thereby promoting tumor progression and further metastasis [24].

Thus, BMDSCs are believed to be the main source of stem cells that cause endometriosis outside the abdominal cavity, in particular, they explain the rare cases of endometriosis in men [25, 26].

The main driving force behind the current understanding of endometriosis has been the discovery that somatic mutations in cancer-related genes are frequently found in endometriosis [27, 28]. However, unlike cancer cells, endometrioid cells have limited proliferative activity. Research by the authors Anglesio et al. in 2017 [29] showed that up to 83% of benign endometriotic lesions contained somatic mutations, and 26% inherited cancer-associated mutations, including those in the KRAS, PIK3CA, ARID1A, and PPP2R1A genes. These well-known genes also frequently exhibit mutational activity in endometrioid and endometrioticovarian cancer [30, 31]. The actual question remains whether these mutations are associated with the development of endometriosis. The answer to this question is tricky, as recent studies have shown that some normal endometrial glands contain somatic mutations in

cancer-related genes, such as KRAS [32]. Thus, these mutations, while characteristic of cancer, may serve as markers of clonality that are useful for linking endometriosis to mutated stem cells in the endometrium, but otherwise have little biological significance. Moreover, malignant cell transformation requires multiple mutations that cause cancer [33].

Immunohistochemical examination of endometriotic foci with and without KRAS mutations found that there were no differences in Ki-67 and phosphorylated AKT levels between foci with and without KRAS mutations [34]. These data support the fact that malignant transformation of endometriosis to cancer is extremely rare, although large endometriotic ovarian cysts may carry an increased risk due to their large number of epithelial cells [35, 36]. However, some studies have shown that increased KRAS activity can promote sustained ectopic endometrial survival and apoptosis resistance when treated with progesterone (P4) [37, 38]. KRAS activation also results in aberrant overexpression of SIRT1 / BCL6, promoting progesterone resistance through inactivation of the GLI1 promoter [39]. Let-7 miRNA usually binds to the 3 'untranslated region of KRAS transcripts, which leads to degradation of KRAS mRNA and suppression of its expression. A polymorphic variant of KRAS is observed in women with endometriosis, including the Let-7 microRNA binding site, which is associated with an increased level of KRAS expression [40].

Numerous studies have compared somatic cancer-mediated mutations at foci of endometriosis and found PTEN mutations in most cases. PTEN is a tumor suppressor gene with a clear association with ovarian cancer where proper regulation of the PI3K enzymatic pathway is required. This pathway is critical to endometriosis oncotransformation [41]. Other studies have found no mutations in the TP53 or PIK3CA genes, and the KRAS mutation has been identified in deep infiltrating lesions of endometriosis, which very rarely undergo malignant transformation, making the correlation between cancer mutations and the development of endompetriosis-associated cancer unclear [42].

The ARID1A gene encodes a protein that is involved in SWI / SNF-mediated chromatin remodeling. Lack of expression due to suppression or mutation is observed in the cells of endometriotic foci. ARID1A plays an important role in many biological processes, including transcription, DNA methylation, and repair of DNA damage [43]. Mutations in the ARID1A gene (SWI / SNF family) lead to a decrease in BAF250a expression. ARID1A is classified as a tumor suppressor gene, and inactivating ARID1A mutations are found in many human carcinomas, most commonly in cancers of the female reproductive system, including endometrioid cancer of the uterus, clear cell ovarian cancer, and endometrioid ovarian cancer [44, 45, 46]. Thus, genes and signaling pathological pathways associated with endometriosis-associated ovarian cancer include PTEN, CTNNB1, PIK3CA, SRC, KRAS, ARID1A, which are known to play a key role in the recurrence of epithelial ovarian cancer. The TP53 gene is one of the best known tumor suppressors, and mutations in TP53 are present in up to 50% of ovarian cancers.

Aberrant methylation of promoter regions of genes ESR1, ESR2, PGR, NR5A1, CYP19A1, HOX, GATA family, with corresponding changes in gene and protein expression, is associated with endometriosis [47, 48, 49, 50]. It is assumed that these genes form a complex signaling network involved in the pathogenetic mechanisms of endometriosis development. It is known that GATA2 hypermethylation and GATA6 hypomethylation stimulate a decrease in the expression of PGR, ESR1,

MMP11, and ALD1A2 and an increase in the expression of HOXC6, CYP19A1, ESR2, NR5A1 [51]. Overexpression of NR5A1 and GATA6 in endometrial stromal cells can also affect E2 synthesis. This mechanism contributes to the development of endometriosis [52]. DNA methyltransferase DNMT3b is a key link in changing the nature of DNA methylation in phenotypically altered cell cultures. It is assumed that the inability of endometriotic stromal cells to suppress DNMT3b activity leads to changes in the methylation of promoter genes and stepwise gene overexpression in endometriosis [53, 54].

The Role of the Inflammatory Process

To date, it is known that local inflammation and dysregulation of the immune system are concomitant signs of endometriosis [55]. The inflammatory aspect of endometriosis is fundamental to the development of new methods for the diagnosis and treatment of this disease. There is an assumption that inflammation is caused by hemorrhage and tissue damage due to the invasive-proliferative and cyclical nature of the vital activity of endometriotic foci. However, it is worth noting that although endometriosis can respond to cyclical changes in estrogen and progesterone, degenerating endometriotic tissue, unlike normal endometrium, does not undergo the same mechanisms as normal during menstruation. Thus, blood accumulates in the foci of endometriosis, especially in endometrioid ovarian cysts, which then undergo degradation and cause the Fenton reaction [56]. This leads to the production of reactive oxygen species, which initiate cell death, inflammation and further development of the process. This process is best supported by the presence of numerous hemosiderin macrophages in endometriotic lesions, especially in the wall of endometriotic ovarian cysts.

An important criterion for the diagnosis of the endometriotic process is the presence of an abundance of inflammatory biomarkers. Important markers such as COX-2, IL-1β, IL-8, tumor necrosis factor alpha (TNF-α), PGE2 and E2 are worth noting. All these markers are elevated in endometriotic foci compared to normotopic endometrium [57]. Prostaglandin E2 stimulates aromatase expression in endometriotic stromal cells [58]. Interleukin-6 secretion in vitro is enhanced in ectopic and normotopic endometrial stromal cells in women with endometriosis [59]. A decrease in the ERα / ERβ1 ratio is observed in the proliferative endometrium in patients with endometriosis, suggesting that ERβ1 is involved in the pathogenesis of endometriosis [60].

IL-1β and PGE2 are also markers of endometriotic activity. IL-1β increases the expression of cyclooxygenase-2 (COX-2) and the concomitant production of PGE2 in both eutopic and normotopic endometrial stromal cells. Induction of COX-2 expression and PG secretion by IL-1β is carried out through the transcriptional regulation of the COX-2 gene through the activation of ERK / p38 MAPK-dependent CREB phosphorylation in ectopic endometrial cells and post-transcriptional enhancement of COX-2 mRNA stability. The increased sensitivity of IL-1β-dependent COX-2 expression in endometriotic stromal cells plays an important role in the pathophysiology of endometriosis development [61]. Thus, the endometrium of the uterus in women with endometriosis shows increased levels of COX-2 expression, and the endometriotic tissue has even higher levels of COX-2. IL-1 increases the expression of COX-2 and activates PGE2 [62]. As a result, endometriotic stromal cells have elevated levels of PGE2, which induce the production of estrogen, which in turn promotes a local inflammatory response [63].

Aberrant expression of steroidogenic acute regulatory protein (StAR) in ectopic endometriotic tissues, leading to an increase in progesterone, is associated with the formation of endometriosis. Induction of StAR gene expression by prostaglandin E2 in endometriotic stromal cells is also thought to contribute to the development of endometriosis [64]. Therefore, prostaglandin E2 is an active mediator of the inflammatory process in endometriosis [65].

High estrogen production is a characteristic feature of endometriosis. Expression of the estrogen receptor ERβ can be up to 100 times higher in endometriotic tissue than in endometrium. Defective DNA methylation and other concomitant epigenetic mechanisms are responsible for the high expression of ERβ in endometriosis. ERβ suppresses ERα expression and results in a high ERβ-ERα ratio in endometriotic cells. ERβ presumably mimics prostaglandin production in endometriotic tissues and cells by inducing COX2 expression. Thus, ERβ is a key therapeutic target and diagnostic criterion in endometriosis [66]. B lymphocytes [67], macrophages [68], CD1a + dendritic cells [69], NK killers [70], Foxp3 + regulatory T cells [71] and myeloid suppressor cells [72] are actively distributed in the foci of endometriosis.

The nuclear factor NF-κB plays an important role in the development of endometriosis [73]. Endometrial iron overload in stromal cells is known to activate IKKβ and lead to the production of large amounts of reactive oxygen species that activate the nuclear factor NF-κB signaling pathway [74]. Disulfiram, an inhibitor of the nuclear factor NF-κB, prevents the growth of the endometriotic lesion in an experimental model of endometriosis in rats [75].

Two potential scenarios have been proposed leading to endometriosis-associated ovarian cancer [76]. The first scenario involves extracellular hemoglobin, iron, and heme (from recurrent hemorrhages that occur with endometriosis) that cause cellular oxidative damage by increasing reactive oxygen species with subsequent DNA damage and mutations. The second scenario involves the constant production of antioxidants, which helps maintain the tumor environment. Both options support the theory of redox imbalance.

Levakov S.A. and Gromova T.A. showed that regardless of the presence of signs of epithelial atypia, overexpression of HNF-1β is characteristic of foci of ovarian endometriosis, which confirms the histogenetic relationship between ovarian endometriosis and unicellular adenocarcinomas. In accordance with the results of a prospective study, an algorithm was developed for monitoring and treating patients with recurrent ovarian endometriosis. Correct interpretation of these X-ray diagnostic methods, as well as the results of histological and immunohistochemical studies (with antibodies to Ki-67, Bcl-2, p53 and HNF-1β), as well as the mandatory assessment of the history of each patient, allow predicting the risk of recurrence and neoplastic transformation of ovarian endometriosis and then develop appropriate treatment guidelines [77].

Genetic aspects of oncotransformation play an important role in understanding the mechanisms of malignancy of endometrioid foci. In samples of both endometrioid and normal epithelium, numerous somatic mutations were found in genes that often mutate in ovarian cancer associated with endometriosis. KRAS is frequently mutated in the endometriotic epithelium, with a higher mutant allele

frequency (MAF). MAF assays, combined with multi-regional sequencing, illuminate the spatio-temporal evolution of endometriosis and the uterine endometrial genome. Cancer-associated mutations have been identified in genes ARID1A, PIK3CA, KRAS, PPP2R1A, ARID1B, PIK3R1, PTEN, MLL3, FBXW7 and ARHGAP35 [78].

Although histopathological and epidemiological studies generally regard endometriosis as a benign condition, scientific studies indicate that endometriotic tissue is the source of various forms of ovarian carcinomas, which are collectively known as endometriosis associated cancer. This group of cancers includes type I ovarian cancer characterized by unique molecular genetic changes that differ from type II ovarian cancer (high-grade serous carcinomas) [79]. The risk of developing ovarian cancer in women with long-term endometriosis is two to three times higher than in women without endometriosis, but these data are characteristic only of endometrioid ovarian cysts, not DIE and superficial endometriosis.

Conclusion

Thus, certain types of ovarian malignancies are associated with endometriosis, and they arise from a pre-existing endometriotic ovarian cyst. These tumors include ovarian clear cell carcinoma, ovarian endometrioid carcinoma, and ovarian seromucinous tumors. These tumors are characterized by common molecular genetic changes that include the ARID1A, PI3K and PP2A pathways, but also have unique molecular changes such as microsatellite instability and CTNNB1 mutations, overexpression of HNF-1β. Given the availability of PI3K inhibitors, this could be a potential target for targeted therapy [80].

Despite recent advances, fundamental problems in understanding and diagnosing endometriosis remain unresolved. A key step in further understanding the pathogenetic mechanisms of endometriosis will be the identification of as yet unknown circulating epithelial progenitors or stem cells that are responsible for epithelial regeneration in both the endometrium and endometriotic foci. It will be equally important to determine the origin of these precursors and to explore their use as biomarkers for predicting endometriosis risk and response to treatment.

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