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Endometriosis: A Malignant Fingerprint

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Abstract

Background: Endometriosis is complex, but identifying the novel biomarkers, inflammatory molecules, and genetic links holds the key to the enhanced detection, prediction and treatment of both endometriosis and endometriosis related malignant neoplasia. Here we review the literature relating to the specific molecular mechanism(s) mediating tumorigenesis arising within endometriosis.

Methods: Guidance (e.g. Cochrane) and published studies were identified. The Published studies were identified through PubMed using the systematic review methods filter, and the authors' topic knowledge. These data were reviewed to identify key and relevant articles to create a comprehensive review article to explore the molecular fingerprint associated with in endometriosis-driven tumorigenesis.

Results: An important focus is the link between C3aR1, PGR, ER1, SOX-17 and other relevant gene expression profiles and endometriosis-driven tumorigenesis. Further studies should also focus on the combined use of CA-125 with HE-4, and the role for OVA1/MIA as clinically relevant diagnostic biomarkers in the prediction of endometriosis-driven tumorigenesis.

Conclusions: Elucidating endometriosis' molecular fingerprint is to understand the molecular mechanisms that drive the endometriosis-associated malignant phenotype. A better understanding of the predictive roles of these genes and the value of the biomarker proteins will allow for the derivation of unique molecular treatment algorithms to better serve our patients.

Keywords

endometriosis; tumorigenesis; gynecologic malignancy; molecular malignant fingerprint

1.0 Introduction

Endometriosis, the presence of endometrial tissue outside of the uterine cavity, is a prominent estrogen-dependent gynecological disease that incites chronic pain in women of reproductive age. This tissue is generally morphologically normal but abnormally located, with common ectopic sites including the fallopian tubes, ovaries, and the rectouterine pouch. More far-reaching, endometrial implants have also been visualized along several different sites in the peritoneal cavity as well as within the lungs [1]. Over 6% of women in the United States are estimated to have endometriosis [2], with approximately 176 million women across the world being affected by this gynecological disease [3]. Risk factors for endometriosis include, but are not limited to, family history, nulliparity, early age of onset for menstruation, heavy menstruation, and outflow tract obstruction. As the mean average age of first pregnancy increases, in the United States, the incidence of endometriosis has also increased [4]. The incidence of diagnosis peaks in the early 30s [5] with the surgical diagnosis occurring approximately 4.6 years after the first reported symptoms [6].

In 1927, Sampson described endometriosis-associated ovarian cancers, marking the first association between endometriosis and neoplastic tissue [7]. The endometriosis-mediated molecular pathways have been difficult to elucidate. However, over the past several years, mounting evidence suggests an endometriosis molecular fingerprint that can be linked to certain benign and malignant neoplasia. This review will focus on reviewing the putative molecular fingerprint that drives endometriosis-associated malignant neoplasia.

1.1 Molecular Fingerprint

The specific molecular mechanism(s) mediating the generation of di novo endometriotic lesions and tumorigenesis arising within those lesions has not been clearly elucidated. One of the earliest etiologic hypotheses was described as the retrograde transport theory,

suggesting that endometrial tissue is transported via the fallopian tubes into the abdominopelvic cavity during shedding of menstruation [8], thereby leading to the ectopic foci of the endometrial lesions. Evidence of retrograde menstruation is seen in 76%-90% of women. Although not all women experience retrograde menstruation, women who do are more likely to develop endometriosis, and this likelihood increases further with the concurrent presence of tubal obstruction [9, 10].

Molecular pathways offer further support for the retrograde transport theory of endometriosis. When endometrial epithelial cells reflux into the abdominopelvic cavity, cytokines (e.g. IL-1b, TNFa, and IL-6) released from invading macrophages in turn trigger a Th1 lymphocyte-mediated acute inflammatory response [11–14], and IL-18, released in the peritoneum of women with endometriosis, triggers a Th2 lymphocyte response. The aforementioned pro-inflammatory pathways induce COX2 gene expression via the MAPK pathway, thereby releasing prostaglandins which results in pain [15]. The ectopic endometriotic foci are significantly more responsive than endometrial stroma, suggesting why patients with endometriosis may experience severe pain out of proportion to the size of the endometriotic implants [15]. Other data have demonstrated that in women with endometriosis, there is decreased IL-19 and IL-22, with levels of the cytokines inversely associated to experienced pain [16]. This indicates the key role of these interleukins in the clinical symptoms of endometriosis. Separately, ERK1 and ERK2 were both found to be activated and have increased levels of phosphorylation in women compared to women without endometriosis [17, 18]. Given these enzymes are involved in cellular proliferation, this finding may indicate a potential link between ectopic endometrial tissue and malignancy.

A recent large systemic study comparing differentially expressed genes associated with endometriosis successfully identified 39 overlapping genes correlated with tumor progression in women with endometriosis. Of those genes, two were related to endometriosis: PGR and EGR1 [17]. PGR, a progesterone receptor gene expressed in uterine lining cell proliferation [19], and EGR1, an estrogen receptor gene, were found in all four of the female cancers, ovarian, endometrial, cervical, and breast, with a mutation rate of 4%. It is reasonable to suggest that mutations in these receptors are gain of function, potentially allowing for these receptors to become hypersensitive to estrogen and progesterone. Given that these were the only two endometriosis-related genes to be found mutated in all four types of cancers which exclusively affect women (with the exception of breast cancer), we believe this information can be utilized to find a therapy to limit endometriosis-related malignancies.

C3aR1 is a linker gene found in both endometriosis-related literature and one of the gene expression profiles. However, there is no previous evidence or association of this linker gene with endometriosis. C3aR1 is a g-protein coupled receptor for the chemotaxis C3a of the complement system, which ultimately plays a role in the inflammatory response. Previously, C3aR1 was potentially thought to be a proto-oncogene as this specific receptor is downregulated in melanoma and testicular germ cell tumor cells, leading to a decreased neutrophil and CD4 T-cell response [20, 21] and allowing for unchecked tumor growth. In analysis, C3aR1 was mutated in 3% of samples, with the most common mutations occurring

in breast cancer, followed by ovarian cancer [17] suggesting that mutations in this gene may lead to malignant transformation of endometriosis. Although not previously thought to be associated with endometriosis or gynecological malignancy, C3aR1 may be a critical link in regard to determining the molecular pathway of endometriosis and its relation to malignancy, and thus should be studied in the future.

SOX-17, a transcription factor, has been recently implicated in the connection between endometriosis and women's cancer. SOX-17 normally inhibits b-catenin and MALM3 [22], acting as a tumor suppressor to antagonize the WNT signaling pathway on cellular growth. Therefore, mutations in SOX-17 allow for genetic transcription and translation leading to cellular growth. In the aforementioned large study, SOX-17 had the highest alteration rate (5%) of all the endometriosis genes related to endometrial cancer [17]. Non-mutated SOX-17 was decreased in several tumors, further suggesting its role as a tumor suppressor [23–26]. Low expression of SOX-17 was also associated with poorer outcomes as tumors with decreased levels of SOX-17 were higher grade and advanced stage [27]. More analysis is needed to determine SOX-17's specific relationship to endometriosis-related neoplasia, but early studies show that abnormalities with this transcription factor strongly correlate with malignancy.

PTEN, a tumor suppressor gene involved with cell cycle regulation, can be mapped to locus 10q23-26 [28]. In a recent study, PCR analysis showed 34% of women with endometriosis had a frameshift mutation in the PTEN gene, compared to 0% in controls [29]. Immunohistochemistry also indicated decreased expression of PTEN in women with endometriosis compared to controls [29]. In mice models, knockout PTEN in the surface epithelium of ovaries induced the production of endometriotic lesions, further suggesting the importance of PTEN [30]. Other experiments exemplified that increasing the amount of PTEN in endometrial cells using vectors leads to increased apoptosis of these cells by preventing angiogenesis through VEGF. This replicated the normal endometrial environment and prevented the ectopic distribution of endometrial tissue [31].

ARID1a is a tumor suppressor gene that encodes for BAF250a, a gene in the SWI-SNF chromatin remodeling complex [32]. BAF250a is heavily involved with gene regulation regarding transcription activation and repression. In one study, mutations and deletions of ARID1a were found to be in 46% of ovarian clear cell carcinoma (OCCC) and 30% of endometrioid adenocarcinoma (EAOC), both of which are associated with endometriosis. Interestingly, ARID1a mutations were not found in high grade serous ovarian cancer [32], a neoplasia not related to endometriosis. A separate study found that endometrial implants and OCCC shared common ARID1a mutations [33]. Chene et al discovered that in EAOC or contiguous endometriosis patients with decreased expression of BAF250a, there were increased levels of certain markers such as pAKT and BAX and decreased levels of BCL2, compared to patients with benign endometriosis [34]. Ultimately, even with the potential connections between ARID1a and BAF250a to endometriosis and malignancy, other studies have indicated that mutations in these genes and proteins alone do not cause cancer and can be found in typical endometriosis implants that do not progress to cancer [35, 36]. Therefore, it is important to continue to study ARID1a's impact on this molecular fingerprint to further elucidate and clarify its involvement.

1.2 Clinical Stigmata

Endometriosis features several clinical stigmata that may be associated with severe pain in a subset of women of reproductive age. These clinical symptoms include but are not limited to dysmenorrhea, dyspareunia, and dyschezia. Patients often describe cyclical pelvic pain that intensifies prior to the onset of menses. Dysmenorrhea is the most common self-reported symptom in women with both laparoscopically diagnosed and histologically diagnosed endometriosis [37–39]. The peri-menstrual shedding of the ectopic lining results in localized inflammation and pain. Many women will also experience chronic pain as a result of ectopic adhesions in the abdominopelvic cavity. In addition, a significant percentage of women will report infertility. The American College of Obstetricians and Gynecologists has suggested that endometriosis is detected unexpectedly in 20-50% of all women undergoing fertility treatment who do not have complaints of menstrual pain [40]. Infertility due to endometriosis may be due to the result of chronic inflammation, distortion of the pelvic cavity, obstruction of the fallopian tubes with ectopic implants, and anovulation.

1.3 Diagnosis

The mainstay of diagnosis is direct visualization and biopsy of ectopic lesions (e.g. laparoscopy) [41, 42]. However, there are drawbacks associated with this type of diagnosis. Surgical procedures are invasive and associated with both cost burden to the patient and the potential for adhesion formation. Up to 25% of lesions elude the surgeon due to the heterogenous phenotypical presentation of endometrioid lesions in the peritoneal cavity [43]. Thus often it is the medical history and physical exam that are used for diagnosis in the outpatient setting. However, the variability of clinical presentation has made the accuracy of diagnosing endometriosis through physical exam difficult [42]. The identification of specific biomarkers will improve the accuracy of the diagnosis of endometriosis. Unfortunately, no current biomarkers exist [44]. Given that CA-125 is not specific, its utility as a screening tool has been questioned, but recent reports have proposed that the combination of CA-125 and HE-4 (human epidydimal protein) may be of use in the future [45].

1.4 CA-125

Cancer Antigen-125 (CA-125) is a traditional biomarker that originates from the coelomic epithelia of the uterus, fallopian tubes, and ovaries in the pelvic cavity [46]. This biomarker has been associated with ovarian epithelial cancers [47] and found to be elevated in greater than 80% of ovarian epithelial tumors [48]. Recently, increased levels of CA-125 have been linked with endometriosis, with a study showing women diagnosed with biopsy-proven endometriosis had higher levels of CA-125 during menstruation compared to a control group of women without endometriosis [49, 50].

Furthermore, a positive association between advanced stages of endometriosis and elevated CA-125 in the peritoneal fluid has been reported [49, 50]. CA-125 levels > 30u/mL can be used as rule-in criteria for diagnosis [51]. It is uncommon for Ca-125 to reach above 100u/mL in women with endometriosis [52], but can be elevated as high as 10,000u/mL in cases of endometrioma rupture [48] or when the omentum is involved [53, 45]. It is believed

that ectopic endometrial implantation in the peritoneal cavity releases higher levels of CA-125, resulting in levels above 100u/mL [54]. A case study published serum CA-125 levels to be at 6484 u/mL after palpation of an adnexal mass that was biopsy confirmed endometriosis [45]. Ectopic endometrial glands were found in the, supporting the argument that peritoneal mesothelial cells can shed increased levels of the glycoprotein. A separate case study that also included omental ectopic endometrial implants had markedly elevated levels of CA-125 [53], further suggesting that the increased surface area of soft tissue in the peritoneal cavity may also be responsible for the severely elevated CA-125 levels [45, 53]. The correlation between CA-125 and endometriosis demonstrates that CA-125 can be utilized when diagnosing endometriosis and must be considered in the differential diagnosis when an adnexal mass is palpated on rectal or vaginal exam. However, since CA-125 can be elevated in physiologic states, its efficacy in diagnosing and monitoring malignant ovarian epithelial neoplasms is reduced. Due to the non-specific nature of CA-125, as it is also found in other malignancies such as colon cancer or pancreatic cancer, its use with endometriosis should be accompanied by the patient's clinical history, physical exam, and visual diagnosis.

The specificity of CA-125 levels is enhanced when evaluated in coordination with HE-4 levels. Khodaverdi et al noted that elevated CA-125 and normal HE-4 can be indicative of endometrioma. [45]. Generally, HE-4 is elevated in malignancy [55] and has been shown to be normal in the case of an endometrioma [45]. Therefore, although CA-125 in itself may not be of use to help identify endometriomas, the combined use of CA-125 and HE-4 may be key to effectively differentiating ovarian malignancies and endometriosis in the future.

1.5 Deep Infiltrating Endometriosis

Deep infiltrating endometriosis (DIE), a type of endometriosis defined by ectopic lesions penetrating >5mm into local peritoneal epithelium, is strongly associated with pelvic pain and dysmenorrhea [56, 57]. These symptoms are contingent upon the severity of adnexal adhesions and the presence of infiltration into the vaginal or rectal canal [58]. This subtype of endometriosis differs from standard endometriosis as DIE invades the peritoneal cavity and can distort abdominopelvic structures, whereas superficial endometriosis remains in the epithelia of the cavity. The most common form of DIE is associated with undifferentiated endometrial glandular pattern [59].

DIE is associated with several somatic mutations: ARID1A, PIK3CA, KRAS, and PPP2R1A. These mutations have been correlated with other endometrial related cancer, but current data indicates there is no association with malignancy or malignant transduction. This suggests an intrinsic characteristic of the mutations of this benign subtype of gynecological disease [60]. Interestingly, due to its invasive habits and association with certain genetic mutations, many experts have called to characterize DIE itself as a neoplasm. More research is needed to better understand the molecular behavior of DIE [61].

1.6 Atypical endometriosis

Atypical endometriosis, or endometriosis with dysplastic characteristics, was first described in 1988 [62]. It is believed that repetitive damage and inflammation in ectopic endometrial

foci result in the development of atypical endometriosis and eventually into endometriosis associated ovarian neoplasms [63]. Atypical endometriosis was found in 36% of OCCC and in 23% of endometrial associated adenocarcinoma with direct progression into EAOC, suggesting the potential for improved overall survival and mortality rates of EAOC with enhanced detection of atypical endometriosis [64, 65]. The chronological progression of atypical endometriosis into EAOC is similar to that of atypical endometrial hyperplasia, thus demonstrating its function as premalignant marker [66].

1.7 Endometriosis-Driven Malignant Neoplasia

Although risk of malignancy arising from ectopic endometrial tissue is relatively low, there are known types of gynecological malignancies shown to arise from endometriosis precursors. OCCC and EAOC of the ovary are two of the most common malignant neoplasia associated with endometriosis.

OCCC is the second most common type of ovarian cancer in the world [67]. OCCC often presents as a unilateral pelvic mass that can cause abdominal distension and pain. Originally, it was believed that OCCC arose from either endometriosis lesions or fibroadenomas, and in 2015, it was suggested that endometriosis was the root behind both of these mechanisms [68]. One hypothesized pathway details that atypical epithelial cells arise from previous endometriotic lesions in the ovary prior to progressing into cancer. The second potential mechanism outlines that non-cystic ectopic endometrial implants generate fibroadenomas, which develop atypical cells that develop into OCCC [68]. The nuclear atypia is most commonly characterized by mutations in PTEN, ARID1a, PIK3CA, and p53 [69]. The worse prognosis is associated with ovarian rupture prior to surgery [70]. Commonly, OCCC is treated with platinum-based chemotherapy. However, there is increasing evidence that localized OCCC arising in a focus of endometriosis may be treated with localized radiation therapy using systems like IMRT and SBRT [71].

EAOC comprises 20% of all ovarian cancers [72] and is the most common form of malignancy related to endometriosis [73]. It most often presents with pelvic pain, abdominal distention, pelvic bleeding, and a pelvic mass [74]. There is a close association between atypical endometriosis lesions and EAOC [64]. Multiple studies have found endometriosis within the malignant tissue upon histological review in 40% [75] and 43% [76] of EAOC cases. All of the endometriosis samples were atypical [46], suggesting a link. Continued molecular analysis of EAOC has shown that ARID1a, PTEN, TP53 and KRAS are the most common mutations found in ovarian EAOC [77]. The use of CA-125 as a potential biomarker for EAOC is limited as this subtype of ovarian cancer may not result in CA-125 elevations [78]. When diagnosed, these masses typically tend to be low grade (grade 1 or 2) [79], but are often mistaken for high grade serous carcinomas. Recent evidence has supported the use of WT1 immunohistochemistry staining to help differentiate the two, as serous carcinomas stain WT1 positive and EOCs stain negative [80]. Standard treatment for EOAC involves platinum-taxane combination therapy due to the cancer’s high sensitivity to the chemotherapy. However, the relapse rate is high [80, 81].

A much less common malignancy potentially related to endometriosis is Mullerian adenocarcinoma. Increasing amounts of case studies have unearthed a potential relationship to the development of this extrauterine adenocarcinoma from endometriosis. The locations of these tumors tend to be in common areas of endometriosis, such as the ovaries, fallopian tubes, and rectouterine pouch [82]. Mullerian adenocarcinoma arising from a deep infiltrating endometriotic lesion, and in women with recurrent endometriosis has been reported [83]. The exact mechanism of this malignancy is still unclear and a deeper molecular and pathological analysis is needed.

1.8 Conclusion

Elucidating endometriosis' molecular fingerprint is to understand the molecular mechanisms that drive the endometriosis-associated malignant phenotype. Endometriosis is complex, but identifying the novel biomarkers, inflammatory molecules, and genetic links holds the key to the enhanced detection, prediction and treatment of both endometriosis and endometriosis related malignant neoplasia. In future studies, an important focus may be the potential link between C3aR1, PGR, ER1, SOX-17 and other relevant gene expression profiles and gynecologic malignancies. Further studies should also focus on the combined use of CA-125 with HE-4 as well as the role for OVA1/MIA as clinically relevant diagnostic biomarkers in the prediction of endometriosis-driven tumorigenesis. A better understanding of the predictive roles of these genes and the predictive value of the biomarker proteins will allow for the derivation of unique molecular treatment algorithms to better serve our patients.

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Abbreviations

OCCC	Ovarian Clear Cell Carcinoma
EAOC	Endometrioid Adenocarcinoma
IMRT	Intensity Modulated Radiation Therapy
SBRT	Stereotactic Body Radiation Therapy
DIE	Deep Infiltrating Endometriosis

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