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Review

Endometriosis-associated ovarian cancer: What have we learned so far?

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ABSTRACT

Endometriosis is defined as the presence of ectopic endometrial tissue outside of the uterine cavity, most commonly in the ovaries and peritoneum. It is a complex disease that is influenced by multiple factors. It is also a common gynecological disorder and affects approximately 10–15% of all women of reproductive age. Recent molecular and pathological studies indicate that endometriosis may serve as a precursor of ovarian cancer (endometriosis-associated ovarian cancer, EAOC), particularly endometrioid and clear cell ovarian cancers. Although histological and epidemiological studies have demonstrated that endometriosis has a malignant potential, the molecular mechanism that underlies the malignant transformation of endometriosis is still controversial, and the precise mechanism of carcinogenesis must be fully elucidated. Currently, the development and improvement of a new sequencing technology, next-generation sequencing (NGS), has been increasingly relevant in cancer genomics research. Recently, NGS has also been utilized in clinical oncology to advance the personalized treatment of cancer. In addition, the sensitivity, speed, and cost make NGS a highly attractive platform compared to other sequencing modalities. For this reason, NGS may lead to the identification of driver mutations and underlying pathways associated with EAOC. Here, we present an overview of the molecular pathways that have led to the current opinions on the relationship between endometriosis and ovarian cancer.

1. Endometriosis

Endometriosis is a benign gynecological condition that affects approximately 5%–10% of reproductive-aged women, causing symptoms of chronic pelvic pain, dysmenorrhea, dyspareunia, and infertility [1]. The definition of endometriosis is histological and requires the identification of the presence of endometrial gland and stroma-like tissue outside the uterus [2]. Several theories have indicated that the histogenesis of endometriosis is that effluent flows retrograde through the lumen of the fallopian tubes into the pelvic-peritoneal cavities at menstruation [3,4]. Furthermore, it has the ability to develop distant foci through proliferation, attachment, and invasion of endometrial glandular epithelial tissue to distant organs [1]. The most commonly affected parts of the body include the ovaries, fallopian tubes, bladder, rectosigmoid colon, and myometrium [5,6]. Another theory, the coelomic metaplasia theory, proposes that endometriosis arises from the metaplasia of cells that line the visceral and abdominal peritoneum following hormonal, environmental, or infectious stimulation [7]. A more recent theory supports stem/progenitor cells and bone marrow-derived stem cells in the pathogenesis of endometriosis [8]. However, Anglesio MS et al. identified somatic cancer driver mutations in the glandular epithelium of deep infiltrating endometriosis lesions, and the authors suggested that the stem-cell-related theory requires additional experiments to confirm the rational of a hypothesis [9]. Moreover, Noë M et al. [10] identified 19 mutations enriched in epithelial but not in stromal lesions using droplet digital PCR technology. The authors proposed a new hypothesis that epithelial and stromal components in developing endometriotic lesions co-develop from independent

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progenitors.

As early as 1925, Sampson proposed a potential correlation between endometriosis and malignant transformation [11]. Czernobilsky and Morris described an “intermediate stage” in the malignant transformation referred to as “atypical endometriosis”; it is currently classified by the degree of dysplastic histologic atypia [12]. Notably, endometriosis is considered a potential pre-invasive lesion and is currently classified as a tumor-like lesion under the World Health Organization (WHO) histologic classification of ovarian tumors. Very recently, Tsai FW et al. [13] indicated that patients with pelvic inflammatory disease had a three-fold increase in the risk of developing endometriosis based on the National Health Insurance Research Database (NHIRD) of Taiwan. The underlying mechanism of endometriosis may be associated with three different processes: (1) endometriosis fragments migrate from the uterus through the fallopian tubes during retrograde menstruation, spreading these endometriosis fragments to the peritoneal cavity and implanting on the serosal surface. (2) metaplasia of the coelom and (3) vascular and lymphatic metastatic spread [8,9,14–17].

2. Endometriosis-associated ovarian cancer

Endometriosis is associated with 15%–50% of clear-cell and endometrioid ovarian tumors, and there is a two- to three-fold increase in ovarian cancer in individuals with endometriosis [18–20]. Endometriosis associated ovarian cancer (EAOC) may be developed through different mechanisms compared with non-endometriosis associated ovarian malignancy. In addition, EAOC often presents at an earlier stage and with lower-grade lesions than non-EAOC. To date, many studies, including systematic reviews [21,22] and meta-analyses [1,23], have demonstrated that women with endometriosis might have an increased risk of epithelial ovarian cancer (EOC). Moreover, another study supports the concept that endometriosis is a malignant transformation and that the histogenesis of endometriosis dependent on several factors, including genetic alterations, hormonal, and immunological factors [6]. Recently, Matalliotakis M [24] identified 20 cases of endometriosis-associated ovarian cancer in 1000 women with endometriosis, among which endometrioid cancer (60%) was the most frequent, followed by clear cell carcinoma (20%) and serous and mucinous adenocarcinomas (20%). The authors concluded that women with endometriosis have an increased risk for certain types of ovarian cancers. A nationwide 14-year historic cohort study using the NHIRD of Taiwan reconfirmed the association between endometriosis and an increased risk of EOC and that the risk of EOC in women with endometriosis might be more apparent [25]. In addition, Kok VC et al. [26] demonstrated that ovarian endometriosis is associated with a 4-fold increased risk of ovarian cancer. Moreover, a historical cohort study linking the NHIRD of Taiwan demonstrated that Taiwanese women with endometriosis had a risk of newly developed epithelial ovarian cancer [27]. Molecular evidence suggests that clear cell carcinoma (CCC) and endometrioid ovarian cancer (ENOC) arise directly from endometriotic lesions. More recently, several comprehensive review articles focused on the endometriosis and EAOC [14,28–31] and have highlighted recent updates and advance in the pathogenesis of endometriosis and EAOC based on clinical, genomic, and immunological aspects. However, the molecular mechanism that underlies the malignant transformation of endometriosis remains controversial, and the precise mechanism of carcinogenesis has not yet been clarified. The multiple factors reported in the pathogenesis of endometriosis-associated ovarian cancer are summarized in Fig. 1.

3. Overview of molecular pathways involved in endometriosis-associated ovarian cancer

3.1. Chromatin remodeling pathway

Chromatin-remodeling factors play essential roles in many biological processes and important roles in the regulation of tissue-specific gene expression during development and differentiation. Switch/sucrose non-fermentable (SWI/SNF) is a family of chromatin remodeling complexes. The SWI/SNF complex contains 10–15 biochemically distinct subunits, including members of the AT-rich interaction domain-containing protein (ARID) family. Notably, SWI/SNF chromatin remodeling complex components, particularly ARID1A and 2, are genetically altered in ~20% of all human cancers [32]. Previous studies have indicated that somatic mutations in *ARID1A* are major molecular contributors to clear cell and EAOC [33,34]. The majority of *ARID1A* mutations are frameshift and nonsense mutations and are randomly distributed in the coding regions. One study [35] showed a high frequency of the loss of ARID1A protein expression in clear cell carcinoma and endometrioid carcinoma. As previously discussed, the loss of ARID1A expression and the loss of tumor suppressor function are due to mutations in *ARID1A*. Therefore, the presence of *ARID1A* mutations is regarded as the most important genetic alteration in the malignant transformation of endometriosis. Very recently, Ishikawa et al. [36] suggested that a high frequency of *ARID1A* mutations in endometriosis-related ovarian neoplasms using a method referred to as“liquid microdissection”. They reported somatic mutations in both *ARID1A* and *p53* in 40% of endometrioid carcinomas and 33.3% of clear cell carcinomas. Similarly, our previous study [37] showed *ARID1A* gene mutations in 50% (5/10) of tumor samples. Notably, we have also identified *ARID1A* gene mutations in concurrent atypical endometriosis lesions in 33.3% (2/6) of cases. These results are consistent with a previous study that showed a high prevalence of *ARID1A* mutations in ovarian neoplasms, atypical endometriosis and tumor lesions [38]. In another study, Yamamoto et al. [39] indicated that of the precursor lesions adjacent to the 23 ARID1A-deficient carcinomas, 86% of the non-atypical endometriosis and 100% of the atypical endometriosis, benign, and borderline clear cell adenofibroma components were ARID1A deficient. The authors indicated that the loss of ARID1A protein expression occurs as a very early event in CCC development and frequently coexists with a *PIK3CA* mutation. Accordingly, the presence of *ARID1A* mutations could be used as a potential biomarker of the malignant transformation of endometriosis [38]. As previously described, epidemiological and molecular data have suggested that endometriosis might be a premalignant lesion in CCC and ENOC.

Mutations of the SWI/SNF complexes (*ARID1A*, *ARID2*, *PBRM1*, *SMARCA4*, *SMARCB1*) in human cancers have predominately been identified by whole-exome analysis [40,41]. NGS indicated that the most commonly mutated subunit among 15 different cancers was *ARID1A*, followed by *PBRM1*, *ARID2*, *SMARCA4*, and *SMARCB1* [42]. Liu M et al. indicated that *ARID2* is a tumor suppressor gene commonly disrupted in hepatocellular carcinoma [43]. The loss of ARID2 protein in non-small-cell lung cancer, malignant melanoma, pancreatic cancer, gastric cancer, and colorectal cancer has previously been reported [44–47]. Recently, Oba A et al. [48] demonstrated that *ARID2* mutations may be a therapeutic target for the treatment of hepatocellular carcinoma. Our previous study [37] demonstrated two *ARID2* mutations, p.Q1112*, and p.T814A, in CCC patients and one *ARID2* mutation, p.S1146L, in an ENOC patient. We suggested that the frameshift and nonsense mutations may lead to the loss of BAF200 expression and the consequent loss of its function as a tumor suppressor. Our preliminary data indicates that *ARID2* knockdown promotes the migration of mucinous cystadenocarcinoma (MCAS) cells via wound-healing assay, thereby further confirming that *ARID2* may act as a potential biomarker of the malignant transformation of endometriosis. Further functional assays are clearly required to understand the role of *ARID2* in

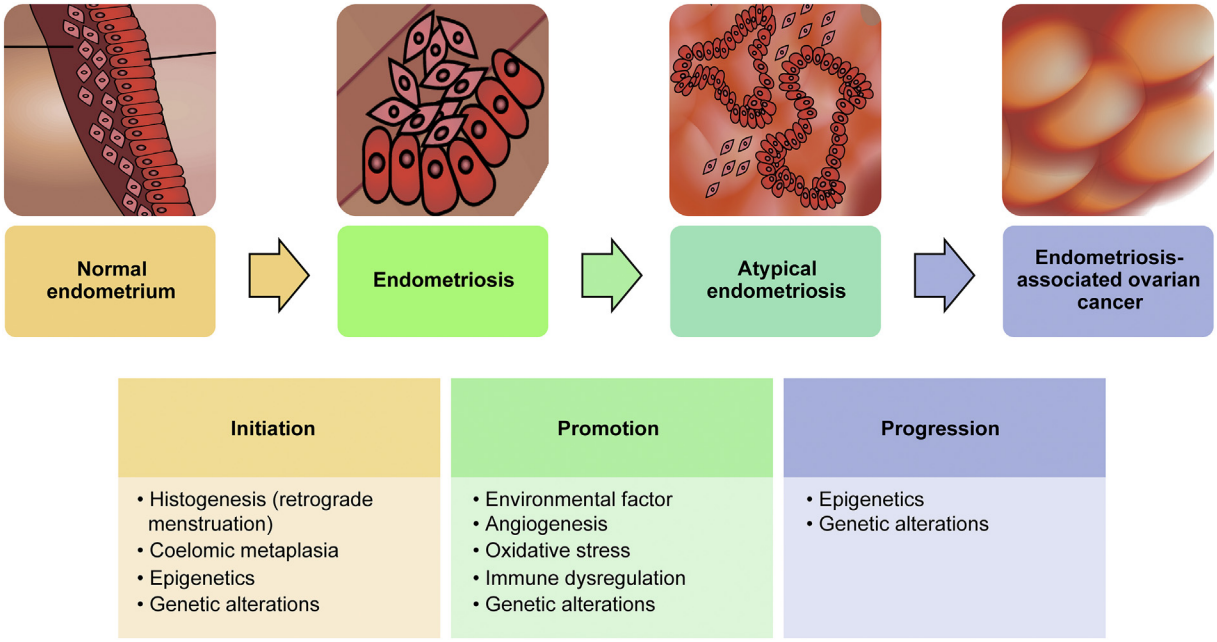

Fig. 1. Overview of the proposed interplay between multiple factors reported in the pathogenesis of endometriosis-associated ovarian cancer.

the pathomechanism of the malignant transformation of endometriosis.

3.2. PI3K-AKT mTOR pathway

PI3K/AKT/mTOR is a signaling pathway in mammalian cells that maintains important cell activities [49]. The phosphoinositide 3-kinase (PI3K) pathway plays a key role in cell proliferation and survival in response to growth factors, hormones, and cytokines. The PI3K pathway is frequently altered in various types of cancer including endometrial, cervical, and ovarian cancers [49]. Furthermore, the PI3K pathway plays an important role in the pathogenesis of CCC [50,51], and the PI3K-AKT-mTOR pathway is a potential target for CCC [52]. *ARID1A* mutations frequently co-occur with other mutations, leading to PI3K/AKT pathway activation [53]. A previous study [54] showed that somatic mutations of the *PIK3CA* gene were detected in 43% of carcinomas, and in all cases, the mutation was H1047R in the kinase domain (Fig. 2A). They also found that the *PIK3CA* mutation p.H1047R was present in the coexisting endometriotic epithelium adjacent to the CCC in 90% of cases. Biochemical assays indicated that the H1047R mutant is differentially regulated by the lipid membrane composition and has a 2-fold increase in lipid kinase activity [55].

Our previous study [37] showed that *PIK3CA* mutations coexisted in tumor lesions and atypical endometriosis in 50% (3/6) of cases. We also determined that the *PIK3CA* mutation p.K111E coexisted in tumor lesions and atypical endometriosis. A very recent study showed that the frequency of somatic mutations in *PIK3CA* was 7/19 (36.8%) in Japanese patients with endometriosis-related ovarian cancer [36] using a specific method referred to as “liquid microdissection”. Although mutations in *ARID1A* and *PIK3CA* are considered early events in the transformation of endometriosis into OCCC, a recent study using whole-exome sequencing indicated there were no significant differences in the frequencies of genetic alterations between the EMS-OSCC and non-EMS-OSCC groups in Korean patients [56].

Stewart et al. [57] demonstrated that *KRAS* mutations were identified in 29% of endometriosis-associated endometrioid adenocarcinoma cases and 3% of tumors that lacked this association. The authors suggested that *KRAS* mutations have an important role in endometriosis-associated endometrioid adenocarcinoma. In another study, Zannoni GF et al. found *KRAS* mutations only in codon 12 (Fig. 2A) but not in codon 13, and *NRAS* and *BRAF* mutations were not found in ovarian CCC [58]. Our previous study [37] showed that the frequency of *KRAS* mutations was 10% (1/10) in the Taiwanese population.

3.3. DNA repair, cell cycle control, and the apoptosis pathway

The proto-oncogene c-*myc* and the tumor suppressor gene *TP53* encode phosphoproteins that participate in the regulation of cellular proliferation, apoptosis, and differentiation [59]. C-myc is a positive regulator of the cell cycle, while TP53 is a negative regulator. In

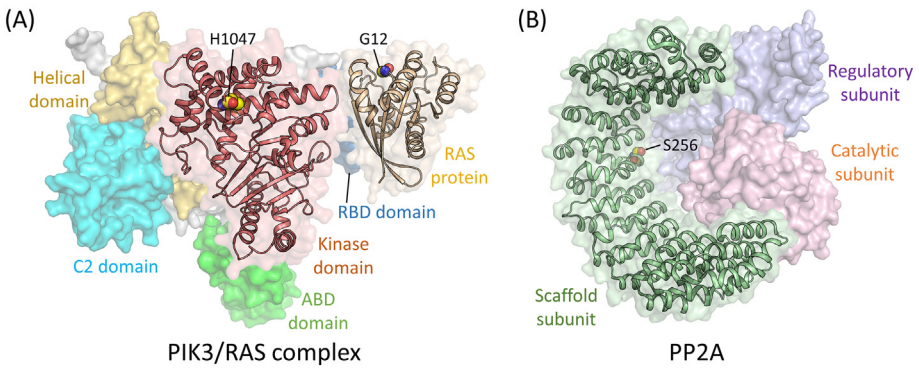

Fig. 2. Ribbon and surface diagrams of the protein structures of (A) the PIK3/RAS complex (PDB ID code 2RD0/1LFD) and (B) PP2A (PDB ID code 2NPP). The most frequent hotspot mutation sites are labeled and shown as spheres. The figure was generated using PyMOL. The PIK3 mutation discussed in this article, H1047R, is located in the kinase domain (red). The RAS mutation discussed in this article, G12V, is located in the P-loop. The PP2A mutation discussed in this article, S256F, is located on the surface of the scaffold subunit (green) at the interface where the scaffold (green) and B regulatory (light blue) subunits interact. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

addition, c-*myc* is one of the most commonly altered genes in human cancer and it may act as a potential therapeutic agent. It has been shown that a c-myc is required during the induction of apoptosis following DNA damage [60]. c-*myc* is often amplified or mutated in ovarian cancer and the amplification of c-*myc* has been reported in approximately 30% of ovarian tumors [61,62].

Most *TP53* mutations in the DNA-binding domain are missense mutations, which suppress p53 transcriptional activity via an inability to bind to p53 responsive elements [63]. Multiple studies have demonstrated that endometriosis harbors mutations in the *TP53* gene [64]. Chromosomal loss of TP53 frequently occurs in severe/late stage endometriosis [65]. Moreover, p53 plays an important role in the malignant transformation of endometriosis. Several published studies have reported no or a very low percentage of *TP53* mutations in CCC, and solitary endometriotic lesions are not associated with carcinoma [66,67]. Our previous study [37] is consistent with the findings that of no or a very low percentage of *TP53* mutations in CCC.

CCCTC-binding factor (CTCF) is a highly conserved zinc finger protein that has various regulatory roles in a cell [68]. CTCF acts as a candidate tumor suppressor, and its ability to bind to the promoter of the oncogene c-myc inhibits its expression [69]. Moreover, CTCF acts as an epigenetic regulator and controls the expression of several genes, including *p53*, *p16* and, *bax* [70–72]. Zhao LT et al. [73] indicated that CTCF is overexpressed in ovarian cancer and is correlated with a poor prognosis in ovarian cancer patients and they also suggested that CTCF may act as a drug target to treat ovarian cancer by interfering with cancer cell metastasis. According to a new study [74], two *CTCF* missense mutations, p.K206E (c.616A > G) and p.H373L (c.1118A > T), were identified in 2/92 (2.2%) endometriotic lesions in the Chinese population. The authors suggested that *CTCF* mutations may be involved in the development of ovarian endometriosis. Taken together, these reports suggest that CTCF plays an important role in the development of ovarian endometriosis and ovarian cancer.

Microsatellite instability (MSI) is a type of genomic instability that is caused by a DNA mismatch repair (MMR) deficiency, which results in the failure to repair errors that normally occur during the replication of repetitive DNA sequences [75,76]. If MMR is impaired, the cells will accumulate an abundance of mutations that may lead to malignant transformations and eventually tumor formation with a hypermutated phenotype [77]. The DNA-MMR enzymes work in pairs, and the formation of the complex is important for their stability [78]. Grass et al. [79] reported MSI in 7 of a series of 56 endometrioid and clear cell carcinomas (12.5%). Recently, Zhao CC [80] demonstrated a sufficient MMR system is associated with improved survival in ovarian cancer. Grassi T et al. [81] demonstrated that a significant loss of MMR proteins was found in the stromal component of endometriotic tissue. They also concluded that the MSH2 expression was higher in the endometriotic tissue than in the eutopic endometrium, which indicates a role of MSH2 in promoting cellular proliferation during oxidative stress. Most recently, Xiao X et al. [82] reported that MMR-deficient ovarian cancer is a unique molecular subgroup. and these patients may be good candidates for anti-PD-1/PD-L1 therapy. Furthermore, Howitt BE et al. [83] demonstrated that a unique subset of CCCs with MSI are associated with enhanced immunogenicity and may be susceptible to an immune checkpoint blockade. Taken together, the previously described studies showed that the MMR system may play an important role in switching the malignant transformation of endometriotic tissue.

PP2A, one of four major serine/threonine phosphatases, is a heterotrimeric phosphatase that contains a R subunit (PR65), a catalytic subunit (PP2Ac), and a B regulatory subunit [84] (Fig. 2B). PP2A regulates various cellular functions, including cell cycle regulation, mitosis, and DNA damage repair [85–87]. Notably, cancer-associated missense mutations have been reported in *PPP2R1A* and *PPP2R1B*, encoding the non-redundant Aα and Aβ subunits. PPP2R1A encodes a scaffolding subunit (A) of the protein phosphatase 2A (PP2A), which is one of the four major serine/threonine phosphatases [84]. The PP2A complex plays a critical role in diverse cellular functions, including the negative regulation of cellular proliferation and potential tumor suppression. *PPP2R1A* mutations have recently been described in 7% of clear cell carcinomas of the ovary [34] and 9.1% of type I ovarian tumors, including low-grade serous, low-grade endometrioid, clear-cell, and mucinous carcinomas [88]. In contrast, Wang F [89] suggested that PPP2R1A mutations are less common in Chinese patients with ovarian cancer than in European and American patients. Furthermore, *PPP2R1B* mutations were absent in ovarian cancer, which suggests that *PPP2R1B* mutations are not actively involved in the pathogenesis of ovarian cancer. Recently, Zou et al. [90] showed mutations in three of 101 ovarian endometriotic lesions, including a *KRAS* p.G12V mutation (Fig. 2A), a *PPP2R1A* p.S256F mutation (Fig. 2B) and two *ARID1A* nonsense mutations, p.Q403* and p.G1926*, using exome sequencing. Based on their findings, the authors concluded that the observations of cancer driver gene mutations in ovarian endometriosis samples support endometriosis as a premalignant disorder. Taken together, these findings showed that PPP2R1A mutations impair PP2A function and enhance tumor formation.

4. Oxidative stress

Oxidative stress refers to the physiological disturbance of the balance between reactive oxygen species (ROS) and the ability of the body to eradicate them. ROS play an important role in the initiation and promotion phases of carcinogenesis. The effects of oxidative stress may lead to the formation of reactive toxic intermediates that may cause DNA damage, such as gene mutations. Multiple studies have shown that several types of antioxidants, such as glutathione, vitamins C and E, and specific enzymes may prevent ROS production or may remove ROS before they can cause harm [91]. Dietary antioxidants may act as cancer preventive agents; however, the results relevant to this question remain controversial [92,93]. Mandai et al. [94] indicated that microenvironmental factors, such as oxidative stress and inflammation are crucial in endometriosis-associated ovarian carcinogenesis. As indicated, endometriosis is characterized by repeated bleeding into the cyst cavity during the menstrual cycle. Notably, iron hemostasis is connected to cancer by multiple mechanisms that involve cancer metabolism, genome stability, and the tumor microenvironment [95]. A previous study [94] showed that free iron concentration was higher in endometriotic cysts than in other benign ovarian cysts. Persistent exposure to highly concentrated free iron may lead to ovarian cancer due to the production of oxidative stress. Most recently, studies have demonstrated that specific targeting of iron metabolism in cancer stem cells (CSCs) may improve the efficacy of cancer therapy [95]. This new theory may shed new light on the potential of CSCs in the treatment of endometriosis-associated ovarian cancer.

5. Environmental factors and microRNAs regulations

Another issue of importance for the presence of endometriosis may be related to environmental factors (EFs) that serve to increase a woman's risk of developing ovarian cancer. Since 1930, polychlorinated biphenyls (PCBs) have been demonstrated as endocrine deregulating agents and widely applied as dielectric fluid in transformers, capacitors, and coolers. Furthermore, the role of human exposure to PCBs in the development of diseases related to hormones has been demonstrated in multiple epidemiological studies [96]. Another chemical agent, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), has been implicated as the most toxic environmental pollutant [97]. In addition, certain PCBs have a biologic toxicity similar to TCDD and are involved in the dysregulation of reproductive function. Several studies have indicated that TCDD may affect the pathophysiology of endometriosis by modulating immune and endocrine functions [98,99]. Rier et al. [100] suggested that TCDD and dioxin-like PCBs promote endometriosis via the stimulation of chronic inflammation and may lead to enhanced estrogen synthesis and

disordering of progesterone-dependent remodeling responses. Furthermore, multiple factors such as elevated levels of phthalate esters, exposure to organochlorine pollutants-, and perflurochemicals, and intrauterine exposure to cigarette smoke, can lead to endometriosis [101]. Moreover, multiple studies have demonstrated that interactions between microRNAs (miRNAs) and EFs play important roles in determining diseases outcome [102]. miRNAs are a class of noncoding RNAs of approximately 22 nucleotides in length that have been found to mediate several processes, such as cell cycle progression, differentiation, development, and apoptosis, and are specifically associated with the pathogenesis of various human cancers [103]. In general, microRNAs are able to prevent mRNA translation and induce mRNA degradation by matching the 3′ untranslated regions of target mRNAs.

Although numerous miRNAs have been demonstrated to be upregulated in ovarian cancers, such as the miR-200 family members miR-200a, miR-200b, miR-200c, and miR-141 [104], there are only few reports on malignant transformations have been published. In particular, tissue inhibitor of metalloproteinase 3 (TIMP3), a proapoptotic protein, is negatively correlated with its target miR-191 [105]. Furthermore, another study demonstrated that miR-196a2 and miR-100 influence endometriosis development [106]. Environmental chemicals may also induce alterations in miRNA expression through inflammation and oxidative stress pathways [107]. Recently, Qiu et al. [108] showed that miRNA-EF interactions are significantly correlated with miRNA characteristics. Abnormalities in miR-449b expression have been shown to contribute to the development and progression of endometriosis [109]. Several studies [110,111] have implicated decreased levels of Let-7 family members in endometriosis tissue, where they are involved in the regulation of several genes, such as *KRAS* and aromatase. Most recently, Sahin et al. [112] suggested that the local treatment of endometriosis with Let-7b is a promising therapy for endometriosis. In a previous report [113], VEGFA acted as a direct and functional target of miR-199a-5p, and the down-regulation of VEGFA decreased ectopic endometrial MSC proliferation, motility and angiogenesis. miR-199a-5p may represent both a diagnostic marker and a therapeutic target for endometriosis. In addition, Dong et al. [114] indicated that the process of EAOC is thought to involve miR-191 by downregulating and lowering the protein expression of the tissue inhibitor metalloproteinases 3. Furthermore, Tian XY et al. [115] showed that the miR-191-DAPK1 axis may play a critical role in modulating the response of ovarian endometriosis and endometrioid carcinoma cells to death inducers. The authors suggested that it may lead to the malignant transformation of endometriosis. Very recently, our study [116] highlighted the role of miR-381-mediated regulation of PIK3CA in the development and progression of ovarian cancer and we suggest that restoration of miR-381 to normal levels in ovarian cancer cells may constitute a therapeutic strategy of patients. Given these findings, a deeper understanding of the interactions between microRNAs and environmental factors could benefit the treatment of endometriosis or EAOC in the near future.

6. Angiogenesis, epigenetics, and immune dysregulation

6.1. Angiogenesis

The importance of angiogenesis was first noted by Folkman in 1971 as highly important during cancer development [117]. Angiogenesis is defined as the formation of new microvessels from existing capillaries. It typically occurs in fetal life however, it also occurs in wound healing and the menstrual cycle in adults as well as in diseases such as diabetic retinopathy, rheumatoid arthritis and endometriosis [118].

When endometriosis is associated with ovarian cancer, tumoral cells require newly formed vessels to obtain oxygen and nutrients necessary for continuous proliferation [119]. Pathological and molecular studies indicate that endometriosis and EAOC could benefit from the role of angiogenesis. Endometriotic lesions produce cytokines and growth factors that regulate proliferation, such as Interleukin (IL)-1b and IL-8, proinflammatory cytokines that induce the chemotaxis of neutrophils and angiogenesis [120], and IL-6, which is known to promote cell proliferation [121] and angiogenesis [122]. Studies have demonstrated that the expression and concentration of vascular endothelial growth factor (VEGF) are increased in tissue from endometriotic patients [123,124]. VEGF is among the most potent and specific angiogenic factors that could contribute to EAOC.

Other proangiogenic factors such as hepatocyte growth factor (HGF) [125], erythropoietin [126], angiogenin [127], macrophage migration inhibitory factor [128], neutrophil-activating factor [129], and TNF-α [130], have been found at increased concentrations in the peritoneal fluid of patients with endometriosis. It could be of interest to know whether concentrations are further elevated in EAOC.

In general, both endometriosis and EAOCs share some of the mediators implicated in inflammatory angiogenesis.

Because endometriosis is a chronic inflammatory disease, tumor-associated macrophages (TAMs) contribute to angiogenesis and immune suppression by modulating the microenvironment. Cancer-associated fibroblasts secrete various proinflammatory factors, such as CXCL12 (SDF-1) and vascular endothelial growth factor (VEGF).

6.2. Epigenetics

The epigenetic modifications involved in EAOC include DNA methylation, histone modifications, and noncoding miRNAs [131]. Studies showed that epigenetic features shared between endometriosis and ovarian malignancy.

DNA methylation is a heritable epigenetic event that occurs at the carbon-5 position of the cytosine within CpG dinucleotide sequences, most frequently leading to gene transcription inhibition [132]. Hypermethylation of genes contributes to oncogenesis when previously activated oncogenes are transcriptionally activated and the protein is active [133]. To this point, several publications have demonstrated that there are common epigenetic alterations between endometriosis and ovarian cancers. Several of the most representative examples of hypermethylated promoters include Runt-related transcription factor (RUNX3) [134], hMLH1 [135], E-cadherin [136], RASSF2 [137] and PTEN [138]. More specifically, Guo et al. [134] demonstrated that 60% of patients with endometriosis and EAOC present with RUNX3 hypermethylation, which results in decreased RUNX3 protein expression. Moreover, these authors suggested that RUNX3 hypermethylation is an early event and occurs gradually during malignant transformation. Similarly, Ren et al. [135] suggested that the hMLH1 aberrant promoter methylation is associated with the malignant evolution of ovarian endometrium. Another study from Ren et al. [137] listed nine candidate genes differentially methylated during the malignant transformation of ovarian endometriosis: RASSF2, RUNX3, GSTZ1, CYP2A, GBGT1, NDUFS1, SPOCK2, ADAM22, and TRIM36.

Histones are fundamental proteins that comprise nucleosomes, which are an important unit of chromatin. Histones can undergo epigenetic modifications, such as acetylation, methylation, phosphorylation and ubiquitylation, that which regulate gene expression. While histone acetylation facilitates gene transcription, histone deacetylation, regulated by histone deacetylases (HDACs), converts chromatin to a more condensed or transcriptionally repressive state and inhibits gene expression [139]. An important study demonstrated that SIRT (a class III HDAC that regulates histone acetylation levels and DNA repair) expression was elevated in epithelial ovarian carcinomas compared to benign tumors [140,141].

6.3. Immune dysregulation

As occurs with other types of cancers, the host's immunological makeup protects against carcinogenesis through a process referred to as “immune surveillance” [142]. Responding to recurrent and invasive endometriotic lesions, dysregulation often occurs in the host's immune

system when it attempts to overcome alterations. This immune dysregulation and dysregulated inflammation are believed to contribute to the formation of endometriosis and EAOC [143,144]. Wendel JRH et al. [145] provide an in-depth review of endometriosis-associated ovarian cancers that develop from the molecular transformation of endometriosis or because of the endometriotic tumor microenvironment. Moreover, women with endometriosis show dysfunctional macrophages, a depressed killing capacity of NK cells, and increased amounts of regulatory T suppressor cells, which contribute to EAOC development [146]. A previous review article indicated that women who developed endometriosis have a defective immune system that lead to an impaired immune response to the endometrial fragments within the pelvic cavity. This article summarizes the potential implications of innate and immune cells in the pathogenesis of endometriosis [147].

One of the first hypotheses is that endometrial fragments released during endometriosis induce inflammation within the peritoneal cavity by neutrophils and macrophages recruited to the area [148], which are then sources of TNF-a, IL-8 [149] and VEGF [150]. Immature dendritic cells (DC) do not exist in the peritoneum of healthy women, while they are present in the membranes of women diagnosed with endometriosis [151]. Nevertheless, the role of DC must be clarified as contradictory results have been published [152,153]. Furthermore, natural killer (NK) cells with decreased cytotoxicity have been found within the peritoneal cavity of woman suffering from endometriosis [154]. Peritoneal macrophages and NK cells in endometriosis have a limited capacity to eliminate endometrial cells or fragments and an imbalance of T cells could lead to aberrant cytokine secretion and inflammation that results in endometrial lesions [155].

High levels of angiogenic factors and cytokine signaling are found in the peritoneal fluid in women with endometriosis as compared to women without the disease [128,156–162]. However, multiple studies have demonstrated the involvement of immune cells in the pathogenesis of endometriosis [163–165]. For example, peritoneal neutrophils and macrophages secrete biochemical factors that promote endometriotic cell growth, invasion, and angiogenesis [155]. Kwak JY et al. [166] demonstrated that when the plasma of peritoneal fluid from women with endometriosis was incubated with neutrophils from disease-free women, the rate of apoptosis was decreased compared to that of control women. This study implied the existence of antiapoptotic factors in the plasma and peritoneal fluid in women with endometriosis.

Suryawansi et al. [167] demonstrated that the complement pathway was the most significantly dysregulated immune pathway in EAOC in a cohort of 120 cases. Notably, 5 complement genes are differentially expressed in control, endometriosis and EAOC. Moreover, the activation of humoral immunity was also identified in endometriosis and EAOC. Furthermore, in vitro results indicated that the KRAS and PTEN/PI3K pathways increased complement gene expression. Taken together, the current studies imply that immunological factors are significantly involved in the pathogenesis of endometriosis and EAOC. A number of promising immune biomarkers may act as potential therapeutic targets for the transition of endometriosis to EAOC in the near future.

7. Advanced technologies are revolutionizing the aspects of the pathogenesis of endometriosis

The next-generation sequencing (NGS) platform will have a significant impact on cancer diagnosis, management and treatment and predicting outcome and response [168]. NGS technology is a feasible and reliable method with that may be used to detect novel and rare somatic mutations. In addition, NGS has been successfully employed to identify germline and somatic mutations in a various of cancers, including gynecological cancers [169], and it can act as a diagnostic method and assisting in the personalized treatment of cancer [170]. In addition, NGS technology has a substantial impact on precision medicine and risk assessment, including early diagnosis, prognosis, and optimization of treatment selection [171,172]. By performing genomic screening via NGS technology, it is possible to identify whether a patient has preexisting genetic conditions that would make them more susceptible to developing cancer in their lifetime [168]. In the recent years, NGS has been utilized to characterize genomic alterations in EAOC. Several studies had demonstrated the utility of NGS in identifying driver mutations in EAOC patients using whole-transcriptome sequencing and targeted sequencing [33,37]. In our previous study, ultradeep ($> 1000\times$) targeted sequencing was performed on 409 cancer-related genes to identify pathogenic mutations associated with EAOC, and candidate genes predictive of malignant transformation were identified [31]. Based on these findings, the identified driver mutations for benign to premalignant lesions could be targets to guide the early diagnosis and prevention of EAOC.

As previously discussed, endometriosis is a disorder in which the endometriotic tissue is outside the uterus, and it is generally assumed to be a benign disease. Moreover, we realized that NGS or ultra-deep sequencing enables the discovery of novel sequence variants. Li XL et al. [173] previously indicated that genetic alterations in cytoskeletal and chromatin-remodeling proteins play an important role in the pathogenesis of endometriosis using whole-exome sequencing. Recently, exome sequencing also yielded promising findings that lesions in deep infiltrating endometriosis, which are associated with virtually no risk of malignant transformation, harbor somatic cancer driver mutations [9]. Although endometriosis is considered to be a benign disorder, the results of NGS technology suggest a new perspective, that the glandular epithelium of deep infiltrating endometriosis lesions harbor well-known cancer-associated somatic mutations. Suda K et al. [174] identified multiple cancer-associated mutations in epithelial cells from ovarian endometriosis and normal endometrium using whole-exome sequencing. They confirmed that *KRAS* and *PIK3CA* were the most frequently mutated genes in endometriotic and normal uterine endometrial epithelium samples using target-gene sequencing. They also indicated that clonal expansion of epithelial cells with cancer-associated mutations leads to the development of endometriosis. These findings strengthen the previous theory that the origin of endometriosis occurs at the genomic level. Very recently, Lac V et al. [175] detected somatic cancer-driver mutations in incisional endometriosis and deep infiltrating endometriosis using a hypersensitive cancer hotspot sequencing panel, including hotspot mutations in *KRAS*, *ERBB2*, *PIK3CA* and *CTNNB1*. Taken together, NGS technology may help us expand our knowledge of the pathogenesis of endometriosis and subvert the classical theory. These studies have implicated endometriosis as a potential premalignant disorder and have indicated it may provide opportunities for diagnostics and therapies in the near future. However, the effect and role of cancer-associated mutations in the pathogenesis of endometriosis must be fully elucidated.

8. Conclusions and future perspectives

Advanced molecular techniques such as NGS technology and droplet-based digital PCR contributes to our understanding of the pathomechanism of endometriosis and EAOC. The mechanism of EAOC is rapidly maturing and will no doubt be part of the future of precise treatment. Most recently, significant advances have been made in the field of the pathogenesis of endometriosis and sequencing analyses are in progress that will incorporate promising technologies for elucidating the mutational landscape of endometriotic lesions. Undoubtedly, these findings bring us towards a new concept in the pathogenesis of endometriosis. Therefore, the application of genetic testing in women with ovarian endometriosis using advance molecular techniques may predict the risk of malignant transformation to ovarian cancer, and the results may influence the clinical decision making in the selection of an appropriate assessment. In conclusion, the current review provides novel insights into the potential mechanisms involved in the progression of endometriosis to adenocarcinoma.

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Declaration of interest

There are no conflicts of interest associated with this paper.

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