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New insights about endometriosis-associated ovarian cancer: pathogenesis, risk factors, prediction and diagnosis and treatment

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Previous studies have shown that the risk of malignant transformation of endometriosis in premenopausal women is approximately 1%, significantly impacting the overall well-being and quality of life of affected women. Presently, the diagnostic gold standard for endometriosis-associated ovarian cancer (EAOC) continues to be invasive laparoscopy followed by histological examination. However, the application of this technique is limited due to its high cost, highlighting the importance of identifying a non-invasive diagnostic approach. Therefore, there is a critical need to explore non-invasive diagnostic methods to improve diagnostic precision and optimize clinical outcomes for patients. This review presents a comprehensive survey of the current progress in comprehending the pathogenesis of malignant transformation in endometriosis. Furthermore, it examines the most recent research discoveries concerning the diagnosis of EAOC and emphasizes potential targets for therapeutic intervention. The ultimate objective is to improve prevention, early detection, precise diagnosis, and treatment approaches, thereby optimizing the clinical outcomes for patients.

KEYWORDS

EAOC, ovarian cancer, pathogenesis, diagnosis, treatment

1 Introduction

Endometriosis is a persistent, non-malignant inflammatory ailment that is subject to estrogenic influence and frequently manifests in conjunction with chronic pelvic pain, dysmenorrhea, and infertility. It is estimated to impact around 5-15% of women in their reproductive years (1). Although endometriosis is typically categorized as a benign condition, it exhibits biological characteristics akin to malignant tumors, including rapid growth, extensive proliferation, angiogenesis. A previous cohort study has shown that the prevalence of ovarian cancer in women with endometriosis is 1.37 times higher compared to the general population (2). Furthermore, previous research has indicated that the

occurrence of malignant transformation in premenopausal women with endometriosis is approximately 1%, while the likelihood of malignant transformation in postmenopausal women ranges from 1-2.5% (3). The connection between ovarian endometriosis and EAOC is believed to be established through the development of endometrial cysts within the ovary (4). Atypical endometriosis (AE) serves as an intermediary stage in which benign lesions evolve into malignant lesions. Women who have a prolonged history of endometriosis are at a heightened risk of developing EAOC, especially if the duration of the disease surpasses 10 years after the initial diagnosis of endometriosis or if there is a frequent occurrence of ovarian endometriosis (5). It is widely acknowledged that the occurrence of EAOC is atypical in instances of ovarian endometriosis, particularly in the clear cell and endometrial subtypes (6, 7).

In 1925, Sampson first outlined the diagnostic criteria for EAOC (8). The etiology of EAOC is commonly ascribed to a variety of complex pathogenic factors, such as endocrine dysregulation, oxidative stress, immune dysregulation, and intricate changes in immune surveillance, ultimately resulting in chronic inflammation (9). The primary objective of this article is to present a thorough examination of the recent progress made in comprehending the pathogenesis of endometriosis malignant transformation. Furthermore, it will explore the most recent research pertaining to the identification of early-stage EAOC, with the ultimate aim of improving prevention, early detection, precise diagnosis, and treatment approaches. We conducted a comprehensive search of the pubmed database to identify research articles pertaining to endometriosis-associated ovarian cancer (EAOC) within the last five years. The search terms employed were “endometriosis malignant transformation” and “endometriosis-associated ovarian cancer.” Only articles presenting complete experimental data and conclusive findings were considered for inclusion, while those with ambiguous or inconclusive research outcomes were excluded.

2 Pathogenesis of EAOC

2.1 Abnormal expression of related genes

Multiple studies suggest that ARID1A may act as a tumor suppressor (10). In their study, Guan et al. made the significant finding that ARID1A operates as a tumor suppressor and engages in an interaction with the P53 protein, thereby impeding cell proliferation through the p53-dependent transcriptional regulation of CDKN1A and SMAD3. The mutations in P53 or ARID1A impede the transcription of tumor suppressors, thereby causing uncontrolled cell proliferation and ultimately resulting in EAOC (11). Recent genomic research and targeted analysis have unveiled frequent mutations in the ARID1A and PIK3CA genes in ovarian clear cell carcinoma, with moderate mutations observed in PPP2R1A and KRAS (12). Similarly, endometrial carcinoma has been discovered to manifest mutations in PTEN, CTNNB1, and KRAS (13). These findings, when amalgamated with gene expression profiling, suggest the activation of the KRAS and PI3K survival pathways and the deactivation of tumor suppressor genes PTEN and ARID1A in clear cell and endometrioid ovarian cancers. Moreover, it is noteworthy that the lack of ARID1A expression, as detected by immunohistochemical analysis, could potentially be associated with ARID1A truncating mutations (14).

Furthermore, the lack of p53 has been observed to lead to an exaggerated proliferation of endometrial glands (15). ARID1A mutations has been hypothesized that this mutation plays a pivotal role as an initial molecular event in the progression of EAOC (16). Prior research has suggested that the presence of ARID1A somatic mutation and subsequent absence of BAF250a protein do not demonstrate a correlation between endometriosis and the ovarian response to chemotherapy (6). The presence of BAF250a is highly correlated with the early stages of carcinogenesis in endometriosis. The lack of ARID1A has been associated with a higher presence of CD8+ tumor-infiltrating lymphocytes (TILs) and intratumoral CD8+ immune cells in EAOC, suggesting the potential effectiveness of targeted immunotherapy in this specific context (17). Furthermore, it has been suggested that the inclusion of supplementary driver events may be imperative for the transformation of ovarian endometriosis with ARID1A loss-of-function mutations (18).

Multiple studies have provided evidence of an increase in the copy number of the CCNE1 gene and an up-regulation of CCNE1 in ovarian clear cell carcinoma. Cyclin E1, in conjunction with the regulatory subunit cyclin-dependent kinase 2 (Cdk2), plays a crucial role in facilitating the transition of the cell cycle from the G1 phase to the S phase. While normal cells tightly regulate cyclin E1 activity, cancer cells exploit its upregulation to enhance the replication of tumor cells. This phenomenon is particularly observed in clear cell carcinomas within EAOC (19).

The frequent activation of the PI3K/AKT pathway in endometrioid and ovarian clear cell carcinomas is a result of mutations in PIK3CA, AKT, and PTEN, leading to their inactivation (20). The presence of PIK3CA mutation, which activates the PI3K/AKT pathway, and the loss of PTEN expression have been extensively documented in around 33 to 40% of ovarian clear cell carcinomas and 40% of endometrioid carcinomas (21, 22). Guan et al. demonstrated that alterations in the PI3K/PTEN/AKT pathway are necessary prerequisites for promoting tumor progression (11). In a separate publication, Gounaris et al. identified the inactivation of the PIK3CA-mTOR and RAS-RAF-MAPK pathways in the eutopic endometrium of endometriosis as a significant contributing factor to the malignant transformation associated with endometriosis (23). Previous studies have provided evidence indicating the advantageous role of Met gene amplification in promoting the malignant transformation of endometriosis. The Met/PI3K/AKT pathway signal plays a significant role in the progression of malignant transformation. Therefore, targeted inhibition of the Met pathway emerges as a potentially promising therapeutic approach for EAOC (24).

The early progression of endometriosis involves the inactivation of the tumor suppressor gene protein phosphatase and tension homologue (PTEN) at locus 10q23.3, as identified in previous research (25). This inactivation is a result of the loss of heterozygosity at locus 10q23.3 and mutation of PTEN, subsequently leading to the activation of the phosphatidylinositol 3-kinase (PI3K) -protein kinase B (AKT) -mammalian target of

rapamycin (mTOR) signaling pathway (26). In the context of endometriosis, atypical endometriosis, and EAOC, the frequent occurrence of loss of heterozygosity resulting in PTEN inactivation suggests a potential continuum between endometriosis and ovarian cancer. Moreover, the presence of somatic mutations in the PTEN gene is highly prevalent in ovarian endometrioid adenocarcinoma, but uncommon in other pathological subtypes (27). Consequently, PTEN has the potential to function as a distinctive molecular alteration in EAOC.

The upregulation of Fibroblast growth factor receptor 2 (FGFR2) expression in ovarian endometriosis demonstrates aberrant elevation during the progression towards malignancy (28). This anomalous expression can be attributed to the occurrence of alternative splicing events within the FGFR2 gene, specifically involving the epithelial FGFR2IIIb subtype (encoded by exon 8) and the mesenchymal FGFR2IIIc subtype (utilizing exon 9). Furthermore, Steele et al. have demonstrated that ligands for FGFR2IIIb have a notable impact on various phenotypes that play a critical role in the growth of epithelial ovarian cancer cells (29). Furthermore, it has been postulated that autocrine FGF7 and paracrine FGF10 signaling cascades could be involved in the augmented epithelial differentiation observed during the course of malignant transformation. Specifically, the upregulation of FGFR2 expression holds the capacity to trigger excessive FGFR2 signal transduction, potentially playing a role in the pathogenesis of endometriosis. Moreover, targeting FGFR2 may present a promising therapeutic strategy for impeding the malignant advancement of endometriosis-associated cancer (refer to Table 1).

2.2 Genetic regulation of miRNA

MicroRNAs (miRNAs) are essential regulators of gene expression. They play a crucial role in functioning as either oncogenes or tumor suppressor genes. Conserved non-coding RNAs, which serve as regulators of target mRNA expression or degradation, have been recognized as potentially influential factors in the malignant transformation of endometriosis (30). As a result, these microRNAs (miRNAs) show potential as biomarkers for both endometriosis and EAOC. The simultaneous evaluation of multiple biomarkers can greatly improve the prognostic predictive value, indicating that a panel of miRNAs may offer a more dependable indicator of disease.

The miR-200 family, particularly miR-200-a and miR-200-b, have garnered significant attention in the field of endometriosis research. Notably, Ohlsson et al. conducted a study that demonstrated a noteworthy decrease in the expression of the miR-200 family, which subsequently led to the occurrence of epithelial-mesenchymal transition, a distinctive hallmark of endometriosis (31). The reduction in ARID1A expression may play a crucial role in the advancement of EAOC in patients who display heightened levels of miR-221 and miR-222 (20). Additional research is necessary to investigate the potential of miR-222 and miR-221 as biomarkers for EAOC. Furthermore, it was observed that miR-143 exhibited upregulation in the serum of patients with EAOC, thereby correlating with heightened cell invasion and migration. This augmented expression of miR-143 consequently results in the suppression of transcription of its target gene FNDC3B, a known facilitator of cell invasion and migration (32).

The association between the cycle of endometriosis and biomarker miR-20a has been extensively studied. Research has provided evidence for the significant role of miR-20a in the pathogenesis of endometriosis, as it directly targets TGF-β and Il-8 (33). A decrease in miR-20a expression results in elevated levels of these cytokines, which may contribute to the promotion of inflammation and tissue repair. By targeting miR-20a to inhibit TGF-β and Il-8, a better understanding of the development of endometriosis lesions could potentially be achieved. It is worth mentioning that miR-20a exhibits up-regulation in ovarian tissues of individuals diagnosed with ovarian endometriosis, thereby playing a role in neovascularization (34). Furthermore, the down-regulation of several mirnas, such as miR-3613-5p, miR-6755-3p (35), let7b, miR-125a (36), and others, has been observed in EAOC tissues. The investigation has provided evidence that miR-191 plays a direct

TABLE 1 Pathogenesis of ovarian cancer associated with endometriosis: abnormal expression of related genes.

Gene	Mechanism	Results	References
ARID1A	Mutation deactivation	Inhibition of the transcription of tumor suppressor factors allows cell proliferation	(10, 11)
PIK3CA	Mutation	The activation of PI3K survival pathway	(12)
KRAS	Mutation	The activation of KRAS survival pathway	(12, 13)
PTEN	Inactivation of tumor suppressor gene mutations	Proliferation of cells	(13, 25–27)
PPP2R1A	Mutation	Proliferation of cells	(12)
CTNNB1	Mutation	Proliferation of cells	(13)
P53	Deletion	Proliferation of cells	(15)
BAF250a	Deletion	It is involved in the early carcinogenesis process	(6)
ARID1A	Deletion	Mismatch repair deficiency and increased CD8+ tumor-infiltrating lymphocytes	(17)
CCNE1	A rise in gene copy number increase and CCNE1	It is involved in cell cycle regulation	(19)
AKT	PI3K/AKT pathway activation	Proliferation of cells	(20–22)
Met	Gene amplification	Met/PI3K/AKT pathway activation	(24)
FGFR2	High expression	Autocrine FGF7 and paracrine FGF10 signal ring	(28, 29)

regulatory role in the expression of TIMP3, thereby influencing cellular proliferation and invasion. TIMP3, a pro-apoptotic protein, exhibits an inverse correlation with cell growth and invasion (37, 38).

2.3 Oxidative stress

The recurrent hemorrhaging and accumulation of heme and free iron within endometriotic lesions are hypothesized to exert a substantial influence on the initiation of ovarian cancer, primarily through the production of reactive oxygen species (ROS) (39). Yamaguchi et al. have reported the high concentration of iron in endothelial cell fluid, leading to the induction of oxidative stress (5, 40). Recent studies have underscored the importance of the interaction between oxidative stress and non-coding miRNAs in the advancement of EAOC (41). *In vitro* investigations have revealed that endometriotic cyst contents manifest an elevated production of ROS and a heightened inclination to elicit gene mutations in comparison to other cyst contents (5). Correspondingly, Sanchez et al. have observed the existence of markers denoting oxidative damage, such as strand breaks, DNA adducts, and lipid peroxidation products, in ovarian cancer tissues (42, 43). The gene expression profile obtained from microarray analysis further substantiates the correlation between oxidative stress and ovarian cancer, particularly in the context of clear cell carcinoma progression (44).

A considerable percentage of the genes displaying elevated expression levels in ovarian clear cell carcinoma are linked to redox processes, including oxidative and detoxification enzymes (45). HNF-1β, acting as a transcription factor, exerts control over target genes responsible for encoding proteins involved in vital cellular processes such as proliferation, differentiation, glucose metabolism, dysplasia, and glycogen synthesis (46). In the domain of ovarian cancer, Liu et al. conducted a study employing the cut HNF-1 beta shRNA strategy, which exhibited heightened susceptibility of ovarian cancer cells to cisplatin and paclitaxel-induced cytotoxicity, both *in vitro* and *in vivo* (47).The accumulation of excessive free radicals can lead to cellular harm and eventual cell demise, whereas the persistent exposure to sublethal ROS, combined with an improved antioxidant status, has the potential to amplify the tumorigenicity of endometriotic cells (48). In a specific study, the utilization of enzyme-linked immunosorbent assay was employed to examine cyst fluid samples collected from a total of 44 patients diagnosed with ovarian endometriosis (OE) and 14 patients diagnosed with EAOC. The expression level of HO-1 is notably reduced in the EAOC group in comparison to the benign OE group, as indicated by the diminished presence of 8-hydroxy deoxyguanosine (8-OHdG) in the fluid. In contrast, the EAOC group demonstrates heightened levels of antioxidants and heme iron in the fluid in comparison to the OE group. It is worth mentioning that HO-1 exhibits the most significant diagnostic efficacy in discerning between benign and malignant cystic fluid, indicating a robust correlation between REDOX imbalance and the malignant progression of endometriosis (49).

The isoforms of GSTM1 are essential in the process of detoxifying harmful substances. Individuals without GSTM1 may have a greater risk of malignant transformation in endometriotic lesions due to insufficient elimination of oxidative stress products (50). Hydroxy-2'-deoxyguanosine (8-OHdG) has emerged as a potential biomarker with promise for evaluating oxidative DNA damage in various disease states. Within the specific context of endometriotic tissues, the up-regulation of 8-OHdG expression has been observed in EAOC when compared to OE. Additionally, CD44, a cell surface receptor responsible for binding to hyaluronic acid, has been demonstrated a potential protective function against DNA damage induced by ROS. The increased production of reduced glutathione synthesis, is accountable for the activation of CD44, specifically the variant isoform (CD44v). In contrast to OE and EAOC endometriotic tissues, a decrease in CD44v expression is evident in EAOC tumor tissues. This decrease, coupled with alterations in CD44v and 8-OHdG, could potentially be associated with the malignant progression of endometriosis (51). The findings of previous studies have provided evidence that electron microscopic replicas of malignant endometriosis cells display mitochondrial swelling and vacuolar alterations, which suggest the possibility of endometriosis lesions growing in a hypoxic microenvironment. These observations imply that the adverse impact of hypoxia on mitochondria could potentially contribute to an increased probability of malignant transformation (52).

2.4 Abnormal gene methylation

Epigenetic modifications, including DNA methylation, histone modifications, and noncoding microRNAs, have emerged as noteworthy factors in the development of EAOC (53), exerting regulatory influence on gene expression independent of alterations in the DNA sequence. Among these modifications, DNA methylation has been extensively studied, with the DNA methyltransferase (DNMT) family playing a pivotal role. Aberrant gene expression and subsequent tumorigenesis can be facilitated by low levels of methylation in cancer gene promoter regions (54). Various studies have demonstrated the involvement of specific genes, such as E-cadherin (CDH1), p16, PTEN, and PTEN hypermethylation in the promoter region, in promoting the malignant transformation of endometriosis (55, 56).

On the other hand, the anomalous hypomethylation of the promoter regions of long interspersed element-1 (LINE-1) (57) and syncytin-1 (58) has been linked to the malignant conversion of endometriosis. The elevated methylation of the hMLH1 promoter region results in the lack of hMLH1 protein expression, a vital constituent of the DNA mismatch repair (MMR) system. This deviation is highly correlated with the malignant advancement of endometriosis (59). The combination of Methylated CpG island amplification and representative difference analysis (DDA) has enabled the discovery of nine candidate genes, namely RASSF2, SPOCK2, RUNX3, GSTZ1, CYP2A, GBGT1, NDUFS1, ADAM22, and TRIM36, that exhibit distinctive methylation patterns associated with the malignant transformation of ovarian endometriosis (60). The transcription factor Runx-related transcription factor 3 (RUNX3), a member of the Runx protein family, plays a crucial role in regulating the self-renewal,

proliferation, and differentiation mechanisms (61). Nevertheless, the current literature presents contradictory results regarding the specific function of RUNX3 in ovarian cancer. For instance, Nevadunsky et al. reported a significant upregulation of RUNX3 and its involvement in promoting the proliferation of epithelial ovarian cancer cells (62). Moreover, Barghout et al. have provided evidence of a significant association between the upregulation of RUNX3 and resistance to RBMO chemotherapy in ovarian cancer cases (63). Conversely, alternative investigations have suggested that the hypomethylation and expression of the RUNX3 gene in epithelial ovarian cancer tissue and cell lines are linked to an unfavorable prognosis (64). Furthermore, these studies have corroborated a positive correlation between elevated RUNX3 methylation and the expression of ER alpha (65). One study proposes that the hypomethylation of the estrogen receptor (ESR) β promoter may potentially contribute to the development of progesterone resistance in individuals with endometriosis (66). Another study reveals a complete absence of ESR and PGR in the EAOC organization (67). However, the present study did not detect any significant alterations in the methylation of ESR and PGR genes when subjected to analysis using MCA - RDA (68).

The tumor suppressor gene RASSF2, which has been recently identified, exerts a notable influence on the Ras signaling pathways. Otsuka et al. have reported that the dysregulated activation of Ras genes leading to the upregulation of RASSF2 may play a pivotal role in the malignant transformation of endometriosis (69, 70). Moreover, Fauvet et al. have emphasized that the activation of the K-ras gene, an oncogene implicated in the Ras signaling pathway, may potentially manifest at a subsequent phase during the progression of malignant transformation in ovarian endometriosis (71). The findings of the study reveal a noteworthy discrepancy in the prevalence of RASSF2 promoter hypermethylation between tumor tissues and ectopic endometrial tissues, with a considerably higher incidence observed in the former. The results of this study indicate that the hypermethylation of the RASSF2 promoter, leading to epigenetic inactivation, may play a crucial role in the early stages of ovarian endometriosis progressing towards malignancy (60) (refer to Table 2).

2.5 Imbalance in hormonal regulation

The absence of progesterone protection in the context of persistent estrogen stimulation presents a potential hazard for the emergence of malignancy in endometriosis (72, 73). The probability of malignant transformation was found to be elevated, as evidenced by a previous investigation conducted by Lavery and Gillmer, wherein the administration of non-antagonistic estrogen as a therapeutic intervention resulted in the malignant transformation of residual ectopic endometrial lesions (74). Moreover, endometriosis fosters a microenvironment that facilitates the excessive accumulation of estrogen via diverse mechanisms (75). Although aromatase is usually not present in endometrial tissue, research has revealed heightened levels of aromatase enzyme activity in ectopic endometrial tissue. This activity facilitates the conversion of androstenedione and testosterone from the ovaries and adrenal glands into estrone and estradiol (E2) (25). Additionally, it is important to acknowledge that ectopic endometrial tissue lacks the enzyme 17β-hydroxysteroid dehydrogenase (17β-HSD), which is typically present in eutopic endometrial tissue. This enzyme plays a pivotal role in the conversion of E2 to estrone, a less potent variant of estrogen. Conversely, 17β-HSD is responsible for the conversion of estrone to the more potent E2, and this enzyme is present in endometriotic tissues. Consequently, the presence of 17β-HSD in endometriotic tissues leads to an augmented production and diminished inactivation of locally hyperestrogenic E2, thereby intensifying its cumulative impact (76). It is noteworthy to emphasize that an excess of E2 can stimulate cell proliferation by facilitating the production of cytokines, particularly IL-8 and RANTES (77). Moreover, the activation of E2 triggers the production of PGE2, thereby promoting the proliferation of tumors. Furthermore, it potentially augments the function of aromatase, thus establishing a reinforcing cycle that sustains the continuous accumulation of estrogen in endometriosis (25). An abnormal accumulation of estrogen in the local area contributes to the progression of normal ectopic endometrium towards dysplasia or potentially malignant transformation (2).

TABLE 2 Epigenetic modifications of gene methylation that occur during malignant transformation of endometriosis.

Gene	Mechanism	Results	References
E-cadherin gene	The promoter region was hypermethylated	Promote the malignant transformation of endometriosis	(55)
p16	The promoter region was hypermethylated	Promote the malignant transformation of endometriosis	(56)
PTEN	The promoter region was hypermethylated	Promote the malignant transformation of endometriosis	(56)
LINE-1	Low methylation in the promoter region of the	Malignant transformation of endometriosis	(57)
syncytin-1	Low methylation in the promoter region of the	Malignant transformation of endometriosis	(58)
hMLH1	The promoter region was hypermethylated	Loss of hMLH1 protein expression, malignant transformation of endometriosis	(59)
RUNX3	Hypermethylation	Poor prognosis	(64)
Estrogen receptor (ESR) beta	Low methylation	Absence of ESR	(66, 68)
RASSF2	The promoter region was hypermethylated	Inactivation of genes	(60)

In the context of EAOC, the endometrioid subtype is predominantly distinguished by the presence of estrogen receptor (ER) and progesterone receptor (PR) expression, while the clear cell subtype generally lacks ER or PR expression. The occurrence of oxidative stress and inflammation due to recurrent bleeding in endometriosis contributes to DNA methylation, which is linked to reduced ER expression (78–80). Previous studies have provided evidence suggesting that the classical ERα signaling pathway experiences significant inactivity during the transition from endometriosis to EAOC, as demonstrated by the downregulation of genes. In contrast, the gene expression of estrogen-associated ovarian cancer (EAOC) in patients with endometriosis demonstrates features of estrogen resistance, as indicated by notably reduced levels of estrogen receptor alpha (ERα) and progesterone receptor (PR), and elevated levels of estrogen receptor beta (ERβ) compared to individuals with normal endometrium. ERβis widely acknowledged for its antiproliferative properties and its antagonistic impact on ERα-mediated proliferation. The impact of ERαto ERβsignaling on the progression of EAOC from endometriosis is contingent upon the specific tissue context. Furthermore, the de-repression of ERαtarget genes, including FGF18, potentially plays a role in the transformation of endometriosis into EAOC (81).

There is a proposition that progesterone exhibits anti-inflammatory attributes within the endometrium. Prior research employing mouse models has provided evidence that inhibiting ERαorβisoforms, coupled with a concurrent decrease in inflammation, effectively hinders the progression of endometriosis (82, 83). Moreover, recent studies have unveiled a noteworthy association between IL-6 and E2 in the advancement of endometriosis (38). Studies have suggested that the estrogen - DNMT1 signaling pathways potentially contribute to the upregulation of RUNX3 methylation, consequently facilitating the malignant transformation of endometriosis (84). Furthermore, there is a suggestion that hormone replacement therapy (HRT) may have the potential to induce malignant transformation in women with a history of endometriosis (85). The risk of adverse effects increases with prolonged usage of hormone replacement therapy (HRT), especially when exceeding a duration of 10 years (86). It is worth noting that available evidence suggests that the use of estrogen alone carries a higher risk of endometriosis malignant transformation compared to the combined administration of estrogen and progestin (85). In contrast, the utilization of hormone replacement therapy (HRT) did not exhibit a heightened propensity for ovarian cancer in postmenopausal women with a medical history of endometriosis or the development of endometriosis (87).

2.6 Imbalance of immune regulation and inflammation

The findings from studies conducted on both human subjects and rats have demonstrated that endometriosis sites display a greater abundance of activated inflammatory cells and cytokines in comparison to the corresponding eutopic endometrium (88). The presence of acute and chronic inflammation is a distinctive characteristic of endometriosis, evident at different stages of tumor advancement, including initiation, malignant transformation, invasion, and metastasis, thereby exerting a substantial impact. Moreover, inflammation disrupts the body's immune surveillance, resulting in the infiltration of immune cells into tumor tissue and engaging in dynamic interactions with cancer cells.

The literature has provided evidence that in individuals with endometriosis, a notable increase in the population of activated macrophages has frequently been observed in the peritoneal fluid (89). Moreover, there has been an observed elevation in the concentration of various essential cytokines and chemokines, such as TNF alpha, beta, IL-1, IL-6, IL-8, regulated upon activation, normal T cell expressed and secreted (RANTES), and monocyte chemotactic protein 1. The chemotactic agent is present in the latter three, resulting in the accumulation of macrophages (90). Additionally, the presence of ferroportin was detected in the epithelium of ovarian endometrioma and clear cell ovarian cancer, while iron-coated M2 macrophages were identified in the stroma of these conditions. The infiltration of epithelial cells into the stroma of ovarian endometrioma suggests the potential participation of iron-coated M2 macrophages in the carcinogenic process of this ailment (91). Research on the quantity and characteristics of macrophages implicated in the malignant progression of endometriosis has consistently demonstrated a reduction in the expression of the antioxidant marker HO-1 in EAOC. This suggests that a diminished presence of M2 macrophages expressing HO-1 may play a significant role in promoting malignancy (92–94).

The substantial involvement of inflammatory mediators and diverse cytokines, including TNF-α, IL-1β, and IL-6, in the initiation, proliferation, and progression of epithelial ovarian cancer, akin to the observations made in endometriosis (95). Szlosarek et al. investigate the role of TNF alpha in the advancement of ovarian cancer, encompassing serous and clear cell subtypes, and observe heightened expression levels of TNF alpha in comparison to normal ovarian tissue. Moreover, previous studies have reported a substantial upregulation of TNF-α mRNA in cultured ovarian cancer cells (96). Further analysis of the same dataset has demonstrated that this increased expression of TNF network genes within the tumor microenvironment leads to augmented signaling pathways associated with inflammation, and NOTCH signaling (97). The observed up-regulation of small inducible cytokine A2 (SICA2) and small inducible cytokine subfamily A member 14 (CCL14) in endometriosis-associated endometrioid ovarian cancer suggests a notable contribution of inflammatory factors in the pathogenesis of both endometriosis and its associated endometrioid ovarian cancer. Prostaglandin E2 (PGE2), a pivotal mediator of the inflammatory response, has also been shown to exert influence on critical mechanisms linked to tumor growth, including cell proliferation, and inhibition of apoptosis (98).

The Nod-like receptor protein structure domain related protein 3 (NLRP3) inflammatory corpuscle is a multifaceted protein implicated in the innate inflammatory immune response. This

intricate assembly encompasses the NLRP3 protein, serving as a detector for inflammasome activation, and the apoptosis-associated speck-like protein containing the CARD complex (ASC). The ASC complex recruits pro-caspase via its CARD domain, thereby facilitating subsequent cascades. The precursor form of caspases is substituted by active caspases, leading to the cleavage of proinflammatory cytokines (precursors of IL-1β and IL-18) into their active states. IL-1β and IL-18, in turn, promote the recruitment of further immune cells associated with inflammation. As a result, the activation of this cancer gene takes place. Consequently, the persistent aseptic inflammation of the NLRP3 signaling pathway potentially functions as the primary phase of carcinogenesis (99). AIM2 functions as a cytoplasmic receptor that identifies double-stranded DNA, particularly originating from viral or bacterial origins, via its carboxyl end hin200 structure domain. This recognition event initiates a series of molecular processes, including the activation of inflammatory proteins and the assembly of AIM2 inflammatory corpuscles. The activation of AIM2 inflammasomes, in conjunction with other conventional inflammasomes, ultimately culminates in inflammatory cell death. In a comparative bioinformatics analysis of endometriosis and ovarian cancer, the immunohistochemical staining analysis further substantiated a robust association between elevated AIM2 expression and heightened Ki-67 activity in clinical samples of EAOC. This discovery lends support to the hypothesis that the alteration of AIM2 and the inflammatory corpuscle in EAOC significantly contribute to the regulation of disease progression.

Anomalous humoral immunity and complement activation significantly contribute to the pathogenesis of EAOC, with cell proliferation serving as a primary mechanism (9). Recent research indicates that there are multiple complement pathways present and operating within the tumor microenvironment, directly stimulating the proliferation of tumor cells and indirectly aiding in immunosuppression and neovascularization (100, 101). The study offers evidence that the activation of Kras and Pten tumor-driven pathways leads to the up-regulation of complement in epithelial cells. The aforementioned findings establish a novel association between the initiation of tumors and immune surveillance facilitated by complement. In conjunction with alterations in immune cells and cytokines, patients with endometriosis commonly manifest heightened activation of B cells. Previous research has established that individuals who have been diagnosed with endometriosis possess the ability to produce systemic antibodies and deposit immunoglobulin G (IgG) and complement in tissues as a humoral response to various autoantigens (102). The mechanism of antibody-induced complement mediated apoptosis efficiently eradicates cells through the classical pathway, which is partially triggered by the attachment of immunoglobulin Fc to infectious agents or diverse antigens found on apoptotic cells. Furthermore, the initiation of this alternative pathway can occur via sequential low-level cleavage of C3 and can be stimulated by various microorganisms such as bacteria, viruses, fungi, and tumor cells. The third complement activation pathway, referred to as the MBL pathway, is activated in response to pathogen-associated molecular patterns (103). Presently, ongoing clinical trials are investigating the focused inhibition of complement as a pharmacological intervention, and the results of these studies will contribute to the development of personalized treatment strategies for patients.

Modifications in immune surveillance might serve as an early indication of the development of cancer in benign conditions (104). Complement signaling can induce diverse immunosuppressive mechanisms, such as the regulation of CD4+ and CD8+ T lymphocytes (105). Furthermore, *in vivo* studies have confirmed the synergistic antitumor impact achieved by combining complement component fragment 5a receptor signaling blockade with PD-L1 antibody, highlighting its reliance on CD8+ T cells (106). On the other hand, the existence of infiltrating T lymphocytes (ITLs), including CD8 + T cells, regulatory T cells, regulatory B cells type II natural killer T cells, and Th2 type CD4 + cells, has been linked to tumor remodeling and potentially aiding tumor growth through immunosuppressive mechanisms (107). These cells possess the capability to hinder the host's anti-tumor response and stimulate angiogenesis within tumors. The impairment of immune cell function and aberrant expression of suppressor T cell response are widely recognized consequences of the interaction between programmed cell death protein-1 (PD-1) and its ligand, programmed cell death ligand-1 (PD-L1), in pathological conditions such as cancer and chronic infection (107). Studies have demonstrated that individuals with endometriosis display elevated levels of PD-1/PD-L1 expression in their circulatory system (108). Moreover, previous research has provided evidence indicating that the upregulation of PD-1/PD-L1 expression occurs in both eutopic and ectopic endometrial tissues among individuals with endometriosis (109). Nevertheless, the precise impact of these immune adaptations on the development and progression of ovarian cancer remains uncertain (108).

Women who have been diagnosed with endometriosis exhibit increased levels of proinflammatory substances, such as tumor necrosis factor-a, interleukin-1b, and interleukin-6. These factors may potentially play a role in the perpetuation of chronic inflammation, thereby promoting the progression and development of EAOC (110, 111). The identification of a heightened frequency of CD8+ cytotoxic T cells has emerged as a promising prognostic determinant in diverse tumor categories, encompassing ovarian cancer (112). These discoveries augment our comprehension of inflammation and immunity as plausible molecular biomarkers for monitoring the advancement of endometriosis towards malignancy, while also offering potential avenues for therapeutic interventions in instances of EAOC. Refer to Figure 1.

3 Prediction and diagnosis of malignant transformation risk factors

3.1 Organizing cytology diagnosis methods

The integration of conventional cytogenetic methods and advanced genetic detection techniques enables the identification of numerical and structural chromosomal abnormalities. However,

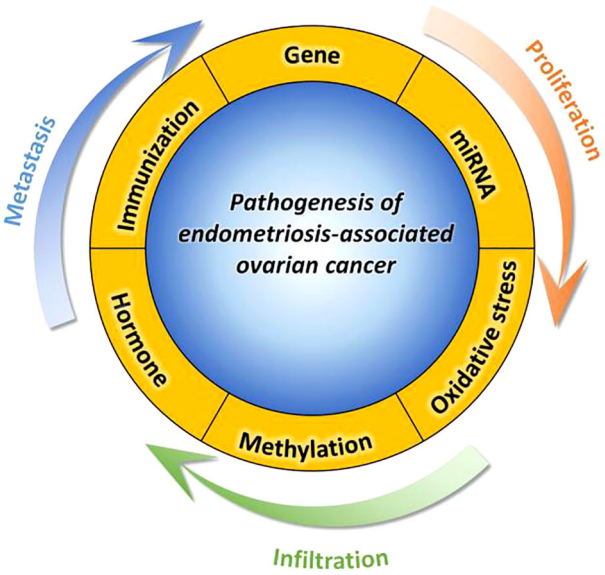

FIGURE 1
This paper aims to provide a comprehensive understanding of the molecular mechanism involved in the pathogenesis of EAOC by examining six distinct aspects, namely abnormal gene expression, miRNA genetic regulation, oxidative stress, abnormal gene methylation, hormone regulation imbalance, immune regulation imbalance, and inflammation.

current literature reports suggest that cytogenetic investigations of individuals with endometriosis often yield inconsistent results. The existing body of research indicates a widely accepted agreement that atypical endometrial hyperplasia encompasses both cellular and structural atypia. However, it is important to note that cellular atypia is more commonly observed in non-cancer patients, whereas structural atypia is more prevalent among patients diagnosed with endometrioid adenocarcinoma (113, 114).

3.2 Serological diagnosis methods

Recent retrospective studies have indicated that preoperative CA125 values are not effective in identifying the malignant transformation of endometriosis (115). Prior investigations have suggested that the assessment of CA19-9, CEA, SLX, and LDH serum levels holds promise as valuable indicators for distinguishing between ovarian tumors related to endometriosis and ovarian endometriosis itself in the preoperative evaluation (116). Arakawa et al. conducted a study in which they observed a specific elevation in serum levels of tissue factor pathway inhibitor 2 (TFPI2) in patients diagnosed with ovarian clear cell carcinoma within the subset of individuals with epithelial ovarian cancer (117). The correlation between CTNNB1 and elevated expression of the HIF1A gene suggests disease advancement, particularly during the initial phases (118). Moreover, the stimulation of AMP-activated protein kinase (AMPK) by TSPAN1 has been shown to promote the development of endometriosis and cellular proliferation (119). TSPAN1 has been recognized as a prospective gene candidate for the screening of high-risk endometriosis, thereby facilitating the advancement of therapeutic pharmaceuticals.

3.3 Imaging diagnostic methods

The ultrasonography assessment of diverse parameters indicates that the recognition of a "vascular solid component" facilitates a notably precise discrimination between benign and malignant endometrioid cysts (120, 121). The initial phase of EAOC may pose considerable diagnostic difficulties due to the lack of a mural nodule. A study has suggested that the identification of cyst wall nodules measuring over 1.5cm in height and with a maximum diameter surpassing 7.9cm could potentially serve as innovative diagnostic markers for distinguishing between EAOC and benign OE with wall nodules (122). Moreover, a retrospective case-control study revealed that several factors, including advanced age, menopause, weight loss, cyst diameter equal to or exceeding 8.33cm, and the presence of solid areas on ultrasonography, were identified as noteworthy risk factors for EAOC (123). Kobayashi et al. reported an increased vulnerability to malignancy in individuals aged 45 years or older, those undergoing menopause, and those with dimensions of 9cm or larger (124). Moreover, the existence of a solid component within the cyst increases the likelihood of developing ovarian cancer associated with endometrial cysts, in line with the findings presented by Kadan et al. (125). Notably, diagnostic studies employing MRI have demonstrated that EAOC typically manifests as a unilocular mass with a low T2WI signal within the cystic component (126). As a result, MRI shows potential as a valuable tool for distinguishing EAOC from non-EAOC and aiding in preoperative diagnoses.

3.4 The development of a diagnostic method

Yang et al. proposed a model that integrates the marker value HE4 and the ADNEX, resulting in increased the discriminatory ability and sensitivity for distinguishing benign from malignant ovarian tumors (127). The application of transvaginal near-infrared (NIR) imaging might provide diagnostic insights into the malignant advancement of endometriosis and could potentially yield further clinical ramifications, and the incorporation of MR relaxation measurements facilitates the identification of conservative therapeutic approaches (128, 129). A pioneering composite optical ultrasound system, employing near infrared guidance and transvaginal ultrasound, is proposed for the purpose of noninvasively quantifying fluid hemoglobin (Hb) levels. The results suggest that metHb is a common form of hemoglobin in benign endometriotic cysts, and the absorption ratio of cyst fluid at 620/580 nm demonstrates significant specificity and positive predictive value. Therefore, it can be utilized as a practical monitoring test for the prompt detection of malignant

transformation in endometriosis (130). Reducing the absorption rate at 620/580 nm could potentially facilitate the identification of individuals necessitating prompt monitoring and surgical intervention, thereby underscoring the significance of clinical assessment in cancer patients.

The Endometriotic Neoplasms Algorithm for risk Assessment (e-NARA) index provides a notable level of specificity in distinguishing between EAOC and benign endometriotic cysts (131). The assessment of intracytothelial iron concentration presents a valuable method for predicting and diagnosing EAOC. The application of proton transverse relaxation time (T2) and T2* (R2) and R2* and relaxation rate in magnetic resonance imaging and optical imaging, including magnetic resonance spectrometry, serves as the exclusive imaging technique (132) for the early anticipation of malignant transformation in molten iron and magnetic resonance (NMR) spectrophotometer. Regardless of age, menopausal status, and cyst size, EAOC exhibits lower R2 values and total iron levels compared to benign ovarian endometriosis cysts. The application of R2 values in distinguishing between EAOC and benign ovarian endometriosis cysts has demonstrated promising levels of accuracy, sensitivity, and specificity (133, 134). Numerous studies have retrospectively evaluated the effectiveness of the Copenhagen index (CPH-I), Risk of Ovarian Malignancy Algorithm (ROMA), and R2 prediction index in forecasting the malignant progression of OE. Notably, the CPH index has been identified as the most reliable predictor for postmenopausal patients with malignant tumors, while the R2 prediction index outperforms other indicators in distinguishing malignant tumors for premenopausal individuals (135). Machine learning algorithms have been employed for the purpose of constructing risk models with the objective of forecasting the probability of malignant transformation of endometriosis in patients (136).

4 Recent advances in EAOC related treatment

Currently, there is a dearth of established therapeutic interventions for EAOC gene mutations, whereas immunotherapy has exhibited effectiveness in the treatment of EAOC. Extensive clinical trials have been undertaken to investigate the possibility of inhibiting this pathway, encompassing inhibitors that target PI3K, AKT, and mTORC1 (137). In particular, Poly (ADP-ribose) polymerase (PARP) inhibitors have exhibited effectiveness in the treatment of ovarian cancer (138, 139). Anti-VEGF antibodies have been employed in the management of ovarian cancer, including EAOC (140). In a phase 2 clinical trial investigating the efficacy of nivolumab, an anti-PD-1 antibody, for the treatment of platinum-resistant ovarian cancer, the overall response rate was determined to be 15% (141, 142). Furthermore, Lynch syndrome, which is distinguished by germline mutations. Mutations in genes involved in mismatch repair result in a significant prevalence of microsatellite instability, which acts as a biomarker for vulnerability to immune checkpoint inhibitors (143). As a result, individuals diagnosed with clear-cell ovarian cancer associated with Lynch syndrome are more inclined to experience favorable outcomes with the administration of immune checkpoint inhibitors. Preclinical inquiries utilizing cell lines have substantiated the potential of inhibitors that target IL-6/JAK/STAT pathway as a means of therapeutic intervention (144, 145). Moreover, there have been documented reports suggesting that the administration of anti-IL-6 antibody to a mouse model of ovarian clear cell carcinoma leads to enhanced prognosis (146). Moreover, in a mouse model of ovarian clear cell carcinoma lacking the ARID1A gene, the efficacy of combination therapy comprising HDAC6 inhibitors and anti-PD-L1 antibody has been successfully demonstrated (147, 148).Reducing the generation of ROS could potentially aid in the prevention of the malignant progression of endometriosis (149). The findings of a study suggest that exploring the potential of Chk1 inhibitors as a targeted therapy may be a promising treatment approach for patients with clear-cell ovarian cancer, presenting a new opportunity for combination therapy (150).

5 Discussion

Long non-coding RNAs (lncRNAs) and post-translational modifications (PTMs), in the pathogenesis of both endometriosis and ovarian cancer has also been suggested (151). Due to the complex nature of this gynecological disorder and its strong association with tumorigenesis, the mechanisms underlying the origin and development of endometriosis are still not fully understood. Vicente Munoz et al. conducted a study in which they identified plasma metabolites in individuals diagnosed with endometriosis (152). The researchers observed heightened levels of valine, foci, choline-containing metabolites, lysine/arginine, and lipoproteins, while the concentrations of creatinine were relatively diminished compared to women without endometriosis (153). The study will contribute to our understanding of the development of malignant transformation. Additionally, it has the potential to provide a new and effective early diagnostic intervention, thereby improving the chances of successful treatment.

6 Conclusion

The specific mechanisms and strategies underlying carcinogenesis in EAOC remain unclear. Further research will contribute to a more comprehensive understanding of the progression of EAOC. Improving our understanding of the pathogenesis of EAOC will contribute to the identification of individuals most prone to the malignant transformation of endometriosis lesions. This knowledge will support the creation of efficacious preventive measures for women with endometriosis who are at the greatest risk of developing EAOC, as well as the

formulation of innovative therapeutic approaches for those diagnosed with EAOC.

Author contributions

BC: Writing – original draft. LZ: Conceptualization, Writing – review & editing. RY: Data curation, Writing – review & editing. TX: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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