The recent progress and therapy in endometriosis-associated ovarian cancer

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Abstract: Endometriosis-associated ovarian cancers (EAOCs) including endometrioid and clear cell ovarian carcinoma are subgroups of epithelial ovarian carcinomas (EOCs), which is generally acknowledged as the most lethal gynecological malignancy. Endometriosis (ES), a common clinical disease among women, presents with clinical symptoms of pelvic pain, infertility, or adnexal masses with the formation of endometrioma. It has long been considered to be a potential risk factor for developing EOCs, mainly of endometrioid and clear cell subtypes. Here, we compiled data from previous researches on deregulated molecular functions among ES and EOCs using gene set–based integrative analysis to decipher molecular and genetic relationships between ovarian ES and EOCs, especially EAOCs. We conclude that epidermal growth factor receptor (ERBB) and Phosphoinositide 3-kinases (PI3K)-related pathways are important in the carcinogenesis of type I EOCs, including clear cell, endometrioid, and mucinous ovarian carcinoma. Dysfunctional molecular pathways, such as deregulated oxidoreductase activity, metabolism, hormone activity, inflammatory response, innate immune response, and cell–cell signaling, played key roles in the malignant transformation of EAOCs. Nine genes related to inflammasome complex and inflammasome-related pathway were identified, indicating the importance of inflammation/immunity in EAOC transformation. We also collect progressive treatments of EAOC focused on targeted therapies and immunotherapy so far. This summarized information can contribute toward effective detection and treatment of EAOCs in the future.

Keywords: Endometriosis-associated ovarian cancers; Immunotherapy; Inflammasomes; Integrative analysis

1. INTRODUCTION

Ovarian cancer, originating in the ovaries or its adnexal organs, with the ability to invade or spread to other parts of the body, is one of the most common gynecologic cancers. It ranks third after cervical and uterine cancers and has the highest mortality rate.[1] The disease typically presents at a late stage when the 5-year relative survival rate is only 29%.[2] Epithelial ovarian cancer (EOC) is the most predominant pathologic subtype (>90%) apart from stromal tumors (5%–6%) and germ cell tumors (2%–3%) of ovary. EOCs have been classified into five major subgroups based on histology, including high-grade serous carcinoma (HGSC; 70%), clear cell carcinoma (CCC; 10%–15%), endometrioid carcinoma (EC; 10%), mucinous carcinoma (MC; 3%), and low-grade serous carcinoma (LGSC; <5%) that differ in origination, pathogenesis, molecular alterations, risk factors, and prognosis.[3–5] The precise pathogenesis and carcinogenesis of EOC is not well understood till now

although there were researches on EOCs by way of morphological and genetic studies leading to several hypothesis of origin, particularly for HGSC.[6] Endometriosis (ES), defined as the presence of ectopic endometrial tissue beyond the uterine cavity, is a complex estrogen-dependent inflammatory disease. It is a common gynecologic disorder with an estimated frequency of 5% to 10% among women of reproductive age.[7] It is particularly frequent among women with dysmenorrhea, dyspareunia, adnexal masses with the formation of endometrioma due to accumulation of chocolate-like contents and events resulting in pelvic inflammation, adhesions, chronic pelvic pain, and infertility.[8,9] In 1920s, Sampson[10] was the first to propose a potential correlation between ES and malignant transformation of ovarian carcinoma. With time, the assumed inference of transformation from ES to ovarian malignancy was supported by molecular evidence suggesting that endometriosis-associated ovarian cancers (EAOC), including CCC and EC, arise from endometriotic lesions clinically, genomically, and immunologically.[11–14] Histopathological and molecular data previously suggested that ES has tumorigenesis potential owing to chronic inflammation along with oxidative stress and may play a crucial role in its malignant transformation to EAOC.[15,16] We had reviewed the molecular, genetic, and immunological aspects on the relationship between ES and EAOC through an integrative gene set–based analysis of past studies. We then attempted to sort out the concepts of functional regulation patterns existing among the major four EOC subtypes with the dualistic model of ovarian carcinogenesis,[17] specific molecular pathways involved in the malignant transformation of EAOC,[18] and the role of inflammasome in EAOC carcinogenesis.[19] We also searched several progressive therapies till date apart from common traditional treatments for EAOC, to provide another view in the future.

2. TWO DISTINCT DEREGULATED FUNCTIONAL PATTERNS AMONG THE FOUR COMMON SUBTYPES OF EOCS

An integrative study was executed to make a comprehensive comparison of gene expression profiles of the four common subtypes of EOCs, HGSC, CCC, EC, and MC, to identify if there is any decisive difference. In addition to consolidation of huge amount of microarray gene expression datasets downloaded from the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO) database, 1454 Gene Ontology (GO[20]) term and 674 Reactome pathway[21] of gene-set definitions applied from the Molecular Signatures Database (MSigDB) were utilized,[22,23] to find out and compare the differentially expressed genes (DEGs). Gene set regularity (GSR) indices reflecting the regulatory function defined by corresponding gene set, deregulated GO terms, and decontrolled functions for each subtype from normal control group were used to evaluate the difference of functional regulation between the EOCs and normal control group. The results revealed interestingly that the HGSC group showed most severe deregulated functions apart from the other subtypes on the modified differential rank conservation algorithm.[24] Histograms, heatmap, and dendrogram of GSR indices indicated that the relationships of the CCC and EC groups were the most similar but differed significantly from the HGSC group, while the MC group fall in between.[17] We also divided the four common subtypes of EOCs into two major groups according to our results:[17] the CCC, EC, and MC subtypes were classified as one group and the HGSC subtype was classified individually as the other due to its inconsistent property with a significantly different distribution of pathogenic DEGs from the other three subtype owing to the most serious dysregulated functions. This dualistic phenomenon was similar to another previous classification of EOCs based on the clinicopathological and molecular features: the type I and the type II categories.[25] CCC, EC, and MC belonged to the type I EOC with usual mutations of KRAS, BRAF, ERBB2, CTNNB1, PTEN, ARID1A, and PIK3CA[26–29] and a relatively slow clinical behavior due to their genetic stability compared with HGSC. HGSC with a more aggressive clinical behavior and a poorer cell differentiation than CCC, EC, and MC was classified as the type II EOC with TP53 mutation[26,29] and homologous repair pathway defects (eg, BRCA1, BRCA2, RAD51D, and BRIP1).[30–33] We further investigated and compared the GSR indices among the four EOCs and the normal control datasets by way of hierarchical clustering and statistical method including strained support vector machine (SVM), and exploratory factor analysis (EFA), to find out the underlying networks of deregulated GO terms among numerous variables to classify and predict all their regulatory functional gene set-based patterns as functionome ($p < 0.001$).[17] We found 27 commonly deregulated GO terms and 66 common deregulated reactome pathways among the four subtype groups. Merging of the microarray gene expression datasets of the CCC, EC, and MC groups (CCC–EC–MC group) due to their similar pathogenesis differs from that of the HGSC groups, and establishment of GO tree for the two major classified subgroups provided an integrated intuitional concept of deregulated functions to show the carcinogenesis of EOCs. The first few significant deregulated reactome pathways analyzed by EFA of the CCC–EC–MC group was with regard to ERBB2/ERBB3 signaling and PI3K-AKT pathway primarily, while HGSC group was related to G protein and cell cycle control including apoptosis, cell proliferation, and development. The deregulated GO trees of the CCC–EC–MC group had characteristic components of oxidoreductase activity, channel activity, binding activity, metabolism, chromatin assembly, cell adhesion, PI3K-AKT, and ERBB signaling pathway. The deregulated GO trees of the HGSC group had more dominant

idiosyncrasy consisted of cell cycle deregulation, including apoptosis, cell proliferation, and development. Many pathogenic mechanisms were sure to be involved in the carcinogenesis or play a crucial role in the metastasis of EOCs,[34,35] for example, ERBB-PI3K-AKT signaling pathway.[17] To sum up, integrative analysis of microarray gene expression datasets was executed to seek and make a thorough comparison of the DEGs in the four subtypes of EOC. The two functional regulatory patterns (functionome) were found to meet the dualistic model of ovarian carcinogenesis: the type I EOCs, including CCC, EC, and MC, are usually genetically stable with a relative indolent clinical manifestation; the type II EOCs, mainly HGSC, have a more uncontrolled cell cycle dysregulation with a more aggressive behavior and poor prognosis (Fig. 1).

3. DYSREGULATED MOLECULAR FUNCTIONS INVOLVED IN THE MALIGNANT TRANSFORMATION FROM ES TO EAOC

After confirming the distinct nature of type I EOCs that contain CCC and EC with high similarity, the genome-wide functional analysis of ES, CCC, and EC by trained SVM was performed with machine learning and EFA with GO tree mapping. This was also performed in accordance with Sampson's[36] first narrative of association between ES and ovarian cancer in 1925, and Scott's[37] further definition of EAOC, including CCC and EC, that should have a successional sequence from benign ES. As mentioned earlier,[17] we downloaded the microarray gene expression profiles of ES, CCC, EC and the normal control ovarian samples from the GEO database to clarify a clear distinction among these three diseases based on the distributions of GSR index levels. We found that functional deregulation was in generally worse in ES, CCC, or EC compared with the normal
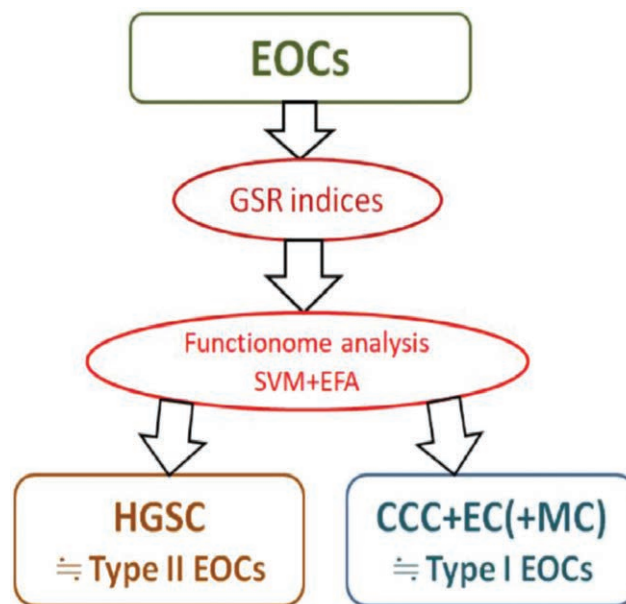

Fig. 1. Two distinct deregulated functional patterns among the four common subtypes of epithelial ovarian cancers (EOCs). We used integrative analysis to calculate and compare four common subtypes of EOCs and then performed functional analysis via support vector machine (SVM) and exploratory factor analysis (EFA). The result revealed the dualistic model of ovarian carcinogenesis: the type I EOCs, including CCC, EC, and MC, and the type II EOCs, mainly high-grade serous carcinoma (HGSC).[17] CCC = clear cell carcinoma; EC = endometrioid carcinoma; GSR = gene set regularity; MC = mucinous carcinoma.

control group, but quite similar within in CCC and EC. This revealed the close relationship between these two cancers and a different pattern of functional regularity in ES from CCC and EC.[18] To find out the significantly deregulated GO terms for the three diseases, we further exploited the methods of EFA along with SVM and constructed the underlying pathogenetic network of numerous variables among ES, CCC, and EC. We sorted out the summaries that deregulated functions of ES included "response to hormone," "binding," "endothelial cell proliferation," "guanosine triphosphatase (GTPase)–mediated signal transduction," "immune response," "protein modification," "regulation of MAPK cascade," and "transport"; deregulated functions of CCC included "immune response," "transport," "oxidoreductase activity," "metabolism," "binding," "GTPase regulator activity," "protein kinase activity," and "chromosome organization"; deregulated functions of EC included "chromosome organization," "channel activity," "binding," "oxidoreductase activity," "transport," "G-protein coupled receptor activity," "immune response" and "GTPase regulator activity," "immune response," "GTPase activity," and "oxidoreductase activity."[18] By comparing the selected coexisting detailed deregulated functions involved in the malignant transformation from these EFA elements and based on the existence of common pathogenesis of the three diseases, we discovered 35 commonly deregulated functions among ES, CCC, and EC related to the following categories: "inflammation response," "immune response," "hormone," "oxidative stress," "metabolism," "transport," "signaling," "cell cycle," etc.[18] In addition to these, there were 71 progressively deregulated GO terms involving malignant transformation that all their GSR indices of deregulated functions went downward from ES to EAOC and trend in rankings with the progression moved upward from ES to EAOC, indicating high consistency with the pathogenesis of EAOC as far as we know.[18,38–40] Another important disclosure was that inflammation, immune-related GO terms, and inflammasome were significantly dysregulated among ES, CCC, and EC though occupying different positions in their functionomes. We could conclude that this data-driven analysis was almost in conformity with most proposed inferences of EAOC pathogenesis and carcinogenesis from previously published researches such as genetic or genomic mutation related to EAOC including PTEN, PI3K, and KRAS in CCC and EC carcinogenesis.[41–43] Immune and inflammation responses such as humoral immunity and complement pathway activation in tumor immune microenvironment leading to cell proliferation,[44] the role of estrogen due to ES as an estrogen-dependent inflammatory disease with the inflammation process contributing to tumorigenesis and progression were involved in EAOC pathogenesis,[45,46] and showed the importance of oxidative stress in the development of EAOC.[18,47] These core deregulated functions, including genetic mutations involved in cell cycle control, inflammation, immune response, hormone activity, and oxidoreductase activity, forming the principle members of EAOC pathogenesis, contribute to the carcinogenesis of EAOC from ES via a crossover interaction with each other (Fig. 2).

4. DYSFUNCTIONAL INFLAMMASOME-BASED MOLECULAR FUNCTIONOME IN CARCINOGENESIS OF EAOC

Similar to many other cancers, EAOCs is a complex disease with multiple causes of pathogenesis, carcinogenesis, and tumor metastasis. We built an integrative bioinformatic platform of functionome-based and data-driven analysis to dissect the molecular pathogenic pathways of EAOC as mentioned above[17,18] and tried to decipher the role of immune response and inflammation in the malignant transformation and cancer progression
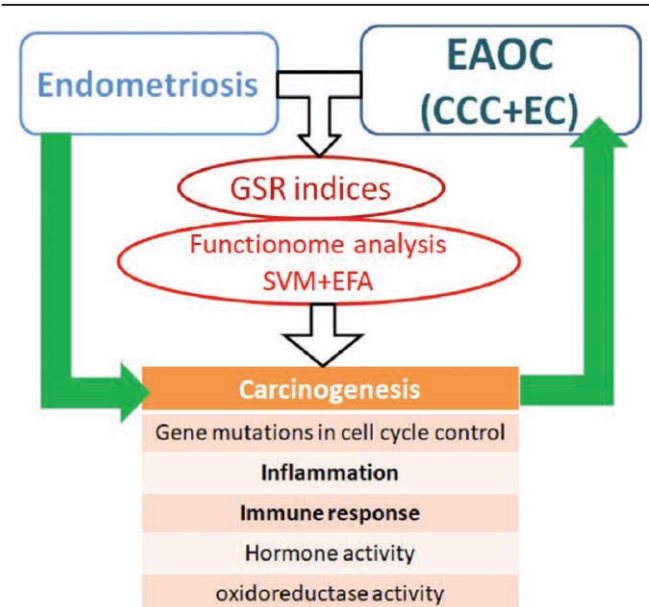

Fig. 2. Dysregulated molecular functions involved in the malignant transformation from endometriosis to endometriosis-associated ovarian carcinoma (EAOC). We used data-driven analysis to investigate the functionomes of endometriosis, clear cell carcinoma (CCC), and endometrioid carcinoma (EC) by trained support vector machine (SVM) and exploratory factor analysis (EFA) with Gene Ontology (GO) tree mapping. The result revealed core deregulated functions, including genetic mutations involved in cell cycle control, inflammation, immune response, hormone activity, and oxidoreductase activity, as mainly carcinogenesis of EAOC.[18] GSR = gene set regularity.

in EAOC because of the causal relationship between ES and EAOC.[10,36] The hypothesis is that ES may have originated from continuous inflammatory responses due to a defective immune system[48–50] and the strong relevance between immunity, inflammation, and cancer.[51,52] Mapping of the GO tree of the immune/inflammation-related GO terms for ES revealed several clusters of deregulated functions including "immune response," "inflammation response," "cytokine production," and "inflammasome complex."[19] Inflammasomes are multimeric protein complexes, which are involved in host inflammation and immunity when being activated, and inflammasome complex and inflammasome-related pathway have been found to be related to tumorigenesis.[53–55] We then checked and correlated seven genes of inflammasome complex (NLRP3, AIM2, PYCARD, NAIP, Caspase-4, Caspase-7, and Caspase-8) and 11 genes of the inflammasome-related pathway (TLR1, TLR7, TOLLIP, NFKBIA, TNF, TNFAIP3, INFGR2, P2RX7, IL-1B, IL1RL1, and IL-18) based on a database created by Gyorffy et al.[56] and the Kaplan–Meier plotter (http://www.kmplot.com/ovar) to investigate the correlation between survival of EAOC patients and the expression levels of inflammasome/inflammasome complex–related genes. We discovered that four of the inflammasome complex genes (NLRP3, AIM2, PYCARD, and NAIP) and five of the inflammasome-related pathway genes (TLR1, TLR7, TOLLIP, NFKBIA, and TNF) presented high expression levels with poor patient survival statistically, indicating the participation of inflammasome complex and inflammasome-related pathways of EAOC progression. By way of a protein–protein interaction (PPI) analysis from the search tool for the retrieval of interacting genes/proteins (STRING) database (https://string-db.org), the nine genes and their corresponding proteins (NLRP3, AIM2, PYCARD, NAIP, TLR1, TLR7, TOLLIP, NFKBIA, and TNF) were confirmed as potential markers for evaluation of EAOC prognosis. Absent in melanoma 2 (AIM2),

a component of the inflammasome complex stated above, could coordinate with other components such as nucleotide-binding domain and leucine-rich-repeat-containing proteins (NLRs) to activate proinflammatory cytokine with their membranes receptors (such as TLR, TNF, INF, and P2RX7) and related pathways to initiate and amplify inflammatory response.[57,58] It was applied in this study for the verification of identified inflammasome-related genes in ovarian cancer transformation via immunohistochemical staining analysis of AIM2 expression among ES and EAOC. The experimental result showed higher expression of AIM2 and higher Ki-67 in clinical EAOC samples than ES samples, with a progressive increasing trend from ES to EAOC, indicating the important role of AIM2 and inflammasome in EAOC transformation and disease progression.[19] We then proposed an operating mode of inflammasome between ES and EAOC based on the study results. In the microenvironment of ovarian ES, specific damage-associated molecular patterns (DAMPs) could cause inflammasome complex to prime active caspase of proinflammatory events via proinflammatory cytokines, leading to inflammation. Subsequently, persistent chronic inflammation activates inflammasome-related genes and oncogene over-expression, inducing carcinogenesis of EAOC. Therefore, dysregulated inflammasomes have played a crucial role in malignant transformation and cancer progression from ES to EAOC and could be regarded as the potential molecular biomarker and the therapeutic target of EAOC (Fig. 3).

5. RECENT PROGRESS IN THE MANAGEMENT OF EAOC

For the past several years, the primary treatment for EOCs or EAOCs remained a debulking operation followed by adjuvant chemotherapy, and then by continuous salvage chemotherapy if the first-line chemotherapy failed or the disease relapsed. However, poor prognosis with decreasing therapeutic efficiency of chemotherapy was ubiquitous in advanced stages (ie, The International Federation of Gynecology and Obstetrics (FIGO) stage III or IV) or recurrence. Therefore, in recent years, the treatment strategy has focused on improving the effect of first-line treatment, particularly enhancing the quality of surgery with aggressive surgical cytoreduction and utilizing better chemotherapy drugs with the addition of targeted therapy or immunotherapy. However, compared with the most common HGSCs, EAOCs, including CCC and EC, are rarer and have the worse clinical prognosis mainly due to their chemoresistant properties. In addition to the modification and application of the technique with primary efficacy of hyperthermic intraperitoneal chemotherapy (HIPEC)[59] with perfusion of intraperitoneal chemotherapy during operation under several accomplished and ongoing clinical trials such as OVHIPEC, OVHIPEC-2, HIPECOVA, and etc,[59,60] adjustment in cycle and frequency of programmed chemotherapy with paclitaxel from a 3 weekly to a weekly schedule with or without weekly carboplatin had its pluses and minuses via worldwide clinical trials (JGOG-3016,[59] GOG-262,[61] MITO-7,[62] and ICON-8[63]). As previously discussed, targeted therapy and immunotherapy need to be further investigated due to the extremely high possible origin of EAOC from ES which is considered generally a complex immune-related and estrogen-dependent disease. With the recent rise in tumor mutational burden (TMB), a biomarker used for assessing susceptibility to immunotherapy, EOCs or EAOC appeared to have an adequate response because of the moderate level of TMB.[64,65] Another novel approach is the use of antiangiogenic drug, bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF)-A, in the first-line treatment combined with chemotherapy and as monotherapy for newly-diagnosed, advanced and platinum-resistant recurrent ovarian
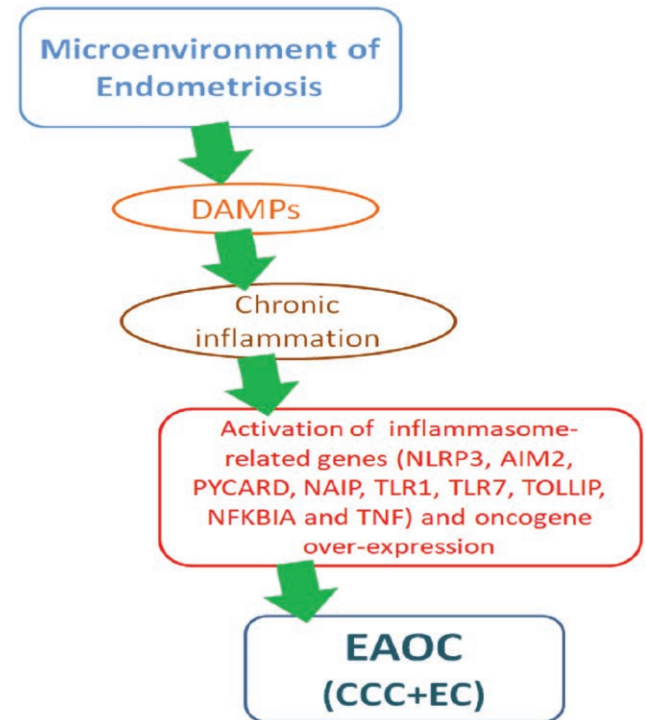

Fig. 3. Dysfunctional inflammasome-based molecular pathogenesis in carcinogenesis of endometriosis-associated ovarian carcinoma (EAOC). The microenvironment of ovarian endometriosis could cause damage-associated molecular patterns (DAMPs) to induce chronic inflammation via inflammasome complex and related response and then activate inflammasome-related genes (NLRP3, AIM2, PYCARD, NAIP, TLR1, TLR7, TOLLIP, NFKBIA, and TNF) and oncogene overexpression, leading to carcinogenesis of EAOC.[19] CCC = clear cell carcinoma; EC = endometrioid carcinoma.

cancer. The results of current clinical trials including GOG-218,[66] ICON-7,[67,68] AURELIA,[69] and GOG-213[70] revealed a notable increase of progression-free survival (PFS), no obvious or slight benefit in poor-prognosis (FIGO stage III with >1 cm residual disease, or FIGO stage IV) patients of overall survival (OS). Other oral VEGF receptor tyrosine kinase inhibitors such as pazopanib and nintedanib were also utilized for maintenance therapy in platinum-sensitive recurrent ovarian cancer with a significant benefit in PFS; however, there was a controversial difference in OS.[71,72] Application of poly-adenosine diphosphate ribose polymerase (PARP) inhibitors for treating recurrent ovarian cancer with a BRCA mutation has shown advantages in recently completed and ongoing clinical trials consisting of SOLO-1, GOG 3005, PRIMA, and PAOLA-1.[73–75] However, the development and implementation of anticancer immunotherapies with immune checkpoint inhibitors including anticytotoxic T-lymphocyte–associated protein 4 (CTLA-4) and antiprogrammed cell death protein 1 (PD-1)/programmed death-ligand 1 (PDL1) antibodies have led to significant improvement in the treatment of various cancers, particularly to counterattack the specific avoidance of immune-mediated recognition and destruction of cancer cells.[76–80] Moreover, clinical trials for aggressive ovarian cancers are currently in progress.[12] Finally, advances in next-generation sequencing (NGS) have made this technology a preferred tool for the diagnosis, management, treatment, monitoring, and predicting the outcome of cancers. Several pathogenic mutations are associated with ES and EAOCs, and these mutations, such as KRAS, BRAF, ERBB2, CTNNB1, PTEN, ARID1A, and PIK3CA, can be used to work together with important results of previous studies and therapies mentioned above to provide deeper insights into potential mechanisms

involved in the progression from ES to EAOC and to lead to more appropriate and precise assessments for EAOC in the future.

ACKNOWLEDGMENTS

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