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Original Article

PPARγ is correlated with prognosis of epithelial ovarian cancer patients and affects tumor cell progression in *vitro*

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Abstract: Background: *Peroxisome proliferator-activated receptor-gamma* (*PPARγ*) is an adopted orphan receptor that belongs to the nuclear receptor superfamily of transcription factors. It plays important roles in regulating adipogenesis, cell growth, proliferation and tumor progression. However, little is known about the function and mechanism of *PPARγ* in epithelial ovarian carcinoma (EOC). Methods: Quantitative real-time polymerase chain reaction (qRT-PCR) was used to measure *PPARγ* levels in 126 EOC tissues and 65 normal tissues. The associations of *PPARγ* expression with clinicopathologic parameters and with overall survival of EOC patients were analyzed by Chi-square test and Kaplan-Meier method respectively. Cox regression analyses were performed to estimate the prognostic values of *PPARγ* and clinical features for patients. In addition, vitro assays including cell proliferation, migration and apoptosis were performed to further explore the biological functions of *PPARγ* in EOC. Results: *PPARγ* was significantly down-regulated in EOC tissues ($P<0.05$). There were significant associations between low *PPARγ* expression and clinicopathological features, such as FIGO stage, distant metastasis and recurrence (all, $P<0.05$). In addition, patients with low expression of *PPARγ* had poorer overall survival than those with high expression ($P = 0.026$). Furthermore, *PPARγ* was an independent prognostic factor in EOC according to Cox regression analysis ($P = 0.037$, HR = 3.037, 95% CI = 1.073-8.797). Aberrant expression of *PPARγ* suppressed cell viability and cell migration and induced cell apoptosis in *vitro*. Conclusion: Our study presents that *PPARγ* is a novel factor involved in EOC progression, which might be a potential prognostic bio-marker and therapeutic target.

Keywords: Epithelial ovarian cancer, prognosis, *PPARγ*, cell progression

Introduction

Ovarian cancer continues to be the fifth leading cause of death in females globally. Epithelial ovarian cancer (EOC), as the most common subtype of ovarian cancer, is the most lethal gynecological malignancy cancer and one of the most common causes of cancer-related deaths among women worldwide [1, 2]. Because of mild and diffuse symptoms or ineffective tumor biomarkers, most patients with EOC are diagnosed at the advanced stages, and the prognosis of these patients is unsatisfactory, even though there has been great improvement on traditional treatments, such as surgery, supplemented with radiotherapy and chemotherapy. According to the previous studies the five-year survival rate was below 40% [3]. Therefore, it is urgently needed to discover new potential molecules to improve clinical outcome of patients suffering from EOC.

Peroxisome proliferator-activated receptor gamma (*PPARγ*) is a member of a nuclear hormone receptor (NR) superfamily and provides have a strong link between lipid metabolism and the regulation of gene transcription [4-6]. NR superfamily is a class of transcription factors which are typically activated by binding to small lipophilic molecules and they play important roles in regulating cell growth, adipogenesis, tissue homeostasis, energy metabolism [7-9], as well as proliferation and tumor progression [10]. *PPARγ* is expressed in various tissues and organs [11]. *PPARγ* signaling is recognized as having a tumor-suppressive effect in terms of growth inhibition and induction of apoptosis or differentiation as well as inhibition

of invasiveness [12-17]. Moreover, *PPARγ* could display anti-tumor effects through inhibition of proliferation and induction of differentiation and apoptosis by targeting the tumor related genes, such as p63, p73, p21, Bax, caspase-3, Bcl-2, c-myc [18-21].

The role of *PPARγ* has been studied in a variety of tumors including colon cancer, leukemia, and gliomas [22-24]. However, the function of *PPARγ* in EOC is still unknown. Thus, in this study, we attempted to investigate the expression level of *PPARγ* in EOC compared to normal tissues, and assess the prognostic value of *PPARγ* in EOC patients, then further study the possible function of *PPARγ* in the EOC cell lines.

Methods and materials

Patients and tissue samples

The study was approved by the Research Ethics Committee of Qilu Hospital of Shandong University, China. Informed consent was obtained from all the participators. All specimens were handled and made anonymous according to the ethical and legal standards.

Binzhou Medical University Hospital. Patients were not subjected to chemotherapy or radiotherapy prior to surgery. A total of 65 normal tissue samples obtained from patients who underwent hysterectomy for benign disease during the same period were used as controls. These samples were immediately frozen in liquid nitrogen and then stored at -80°C until use. The clinicopathological features including age, tumor size, FIGO stage, lymph node metastasis, distant metastasis, and recurrence were collected in a database. All patients were staged based on the International Federation of Gynecology and Obstetrics (FIGO) staging system [25].

Quantitative real-time PCR assay

The expression levels of *PPARγ* in EOC and normal tissues were detected by quantitative real-time PCR assay. Briefly, total RNA was extracted from tissues using TRIzol® (Life Technologies, Carlsbad, CA, USA) according to the manufacturer's protocol. Then, mRNA expression levels were quantitated using an mRNA Assay Kit (Life Technologies) according to the manufacturer's protocol. The two-step protocols included reverse transcription with an mRNA-specific primer and convert mRNA to complementary DNA, following by real-time quantitative PCR with TaqMan® probes. The *GADPH* was used as an endogenous control for mRNAs. Each sample was examined in triplicate and the amounts of the PCR products produced were normalized to *GADPH*.

Cell culture

The ovarian cancer cell line OVCAR3 was purchased from American Tissue Type Collection (ATTC) and maintained in Minimum Essential Medium (Life Technologies) supplemented with 10% (v/v) fetal bovine serum and antibiotics (100 units/ml of penicillin and 100 mg/ml of streptomycin) at 37°C in a 5% CO_2 incubator.

Transfection of plasmid pEGFP-C1-PPARγ

Binzhou Medical University Hospital. Cells were transfected with *pEGFP-C1-PPARγ* using Lipofectamine™ 2000 (Invitrogen) according to the manufacturer's instructions. pEGFP-C1 was used as mock control. Then cells were cultured in normal condition for further analysis.

Cell proliferation assay

Cell proliferation was determined by CellTiter 96® AQueous One Solution Reagent (Promega) according to manufacturer's instructions at different time points (0, 12, 24, 48, and 72 hours). Briefly, 2×10^3 cells per well were seeded in 96-well plates and cultured for 24 h. Then, the cells were transfected with *pEGFP-C1-PPARγ* or pEGFP-C1 respectively. After 8 h, cells were treated with DMSO or TGZs (5 mM) for 24 h, then added 20 ml of CellTiter 96® AQueous One Solution Reagent into each well of the 96-well assay. Subsequently, the cells were incubated at 37°C for 4 h, and recorded the absorbance at 490 nm using a 96-well plate reader. All experiments were performed in triplicate.

Migration assay

OVCAR3 transfected with *pEGFP-C1-PPARγ* or pEGFP-C1 were harvested 48 h after transfection and re-suspended in serum-free MEM. Aliquots (5×10^4 cells/100 μl) of the prepared cell suspension were added into the upper chamber, and the lower chamber was filled with 0.5 ml of media containing 10% FBS. Cells were incubated at 37°C in a humidified incubator with 5% CO_2. After 24 h, no migrated cells were removed from Trans-well membrane filter (Costar, USA) inserts with PBS, migrated cells

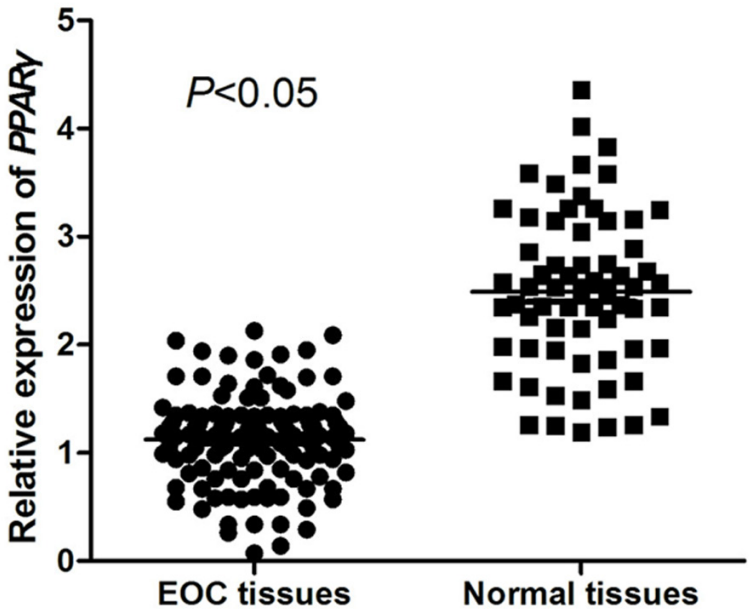

Figure 1. *PPARγ* expression in 126 EOC tissues and 65 normal tissues were respectively detected by qRT-PCR. After normalization to *GADPH*, the expression level of *PPARγ* in EOC tissues was significantly lower than that in normal tissues ($P<0.05$). All data are expressed as mean ± SD and analyzed using Student's t test.

were stained with Kristallvilet for 10 min. Thirty random fields from each experimental group were counted, and the number of cells migrated was calculated. The experiment was repeated three times.

Measurement of cell apoptosis

Cells were harvested 48 hours after transfection, and immunostained with Annexin-V fluorescein isothiocyanate (FITC) and propidium iodide (PI) according to the manufacturer's instructions (Apoptosis Detection Kit, Key GEN). Data analysis was performed using Cell Quest software (BD Biosciences).

Statistical analysis

All analyses were performed using SPSS 18.0 software. Comparisons of *PPARγ* levels between EOC tissues and normal tissues were performed using Student's t test. Correlations between *PPARγ* expression and clinicopathological characteristics were assessed using Chi-square test. Overall survival (OS) was measured for each patient. Survival curves were described using Kaplan-Meier method, and differences between them were estimated by log-rank test. Cox regression analysis was used to estimate univariate and multivariate hazard ratios for prognosis. Difference was considered statistically significant when the *P* value was less than 0.05.

Results

Expression of PPARγ is down-regulated in human EOC tissues

We firstly examined *PPARγ* expression level in 126 human EOC tissues and 65 normal tissues by qRT-PCR. As shown in **Figure 1**, after normalization to *GADPH*, the expression level of *PPARγ* in EOC tissues was significantly lower than that in normal tissues ($P<0.05$). The data indicated that abnormal *PPARγ* expression may be related to EOC pathogenesis.

PPARγ expression and its correlation with clinicopathological parameters of EOC patients

The relationship between *PPARγ* expression and clinicopathologic parameters of 126 patients with EOC was evaluated. As shown in **Table 1**, the level of *PPARγ* expression in EOC was strongly correlated with FIGO stage ($P = 0.018$), distant metastasis ($P = 0.022$) and recurrence ($P = 0.012$). However, there were no significant associations between *PPARγ* expression and other clinical features including age ($P = 0.439$), tumor size ($P = 0.165$), menopause ($P = 0.231$), and lymph node metastasis ($P = 0.469$).

Low expression of PPARγ is associated with poor prognosis of EOC patients

As determined by Kaplan-Meier method, the expression of *PPARγ* in EOC tissues was significantly correlated with overall survival. The log-rank test showed that the survival time was significantly different between groups with high and low expression of *PPARγ* (Log rank test, $P = 0.026$, **Figure 2**), indicating that the low expression of *PPARγ* was correlated with a shorter survival time of patients with EOC. Cox regression multivariate analyses including age, tumor size, menopause, lymph node metastasis, FIGO stage, distant metastasis, recurrence and *PPARγ* expression were performed. The results demonstrated that *PPARγ* expression had a significant correlation with EOC prognosis, and it

Table 1. The relationship between clinicopathological parameters and expression of *PPARγ*

Parameters	No.	*PPARγ* expression		x^2	*P* values
		Low	High		
Cases	126	72	54		
Age (years)					
≤40	58	31	27	0.599	0.439
>40	68	41	27		
Tumor size (cm)					
≤4	61	31	30	1.931	0.165
>4	65	41	24		
Menopause					
Absent	53	27	26	1.436	0.231
Present	73	45	28		
Lymph node metastasis					
Absent	56	30	26	0.525	0.469
Present	70	42	28		
FIGO stage					
I/II	81	40	41	5.577	0.018
III/IV	45	32	13		
Distant metastasis					
No	79	39	40	5.229	0.022
Yes	47	33	14		
Recurrence					
No	85	42	43	6.375	0.012
Yes	41	30	11		

was found to be an independent prognostic factor for patients with EOC after tumor resection (HR = 3.073, 95% CI = 1.073-8.797, *P* = 0.037, **Table 2**).

pEGFP-C1-PPARγ significantly upregulated the expression of PPARγ in EOC cells

To further investigate the role of *PPARγ* of EOC, *pEGFP-C1-PPARγ* was transfected into OVCAR3 cells. pEGFP-C1 was used as a mock control. As shown in **Figure 3A**, OVCAR3 cells transfected with *pEGFP-C1-PPARγ* showed a significant increased mRNA expression of *PPARγ* compared to the mock group (*P*<0.05).

Effect of PPARγ on EOC cell proliferation in vitro

To evaluate the effect of *PPARγ* on OVCAR3 cell proliferation, cells were transfected with *pEGFP-C1-PPARγ* or mock control and cell viability was assessed at 0, 12, 24, 48 and 72 h post-transfection. The inhibition rates increased significantly in a time-dependent manner at 12, 24, 48, and 72 h (*P*<0.05, **Figure 3B**).

Ectopic PPARγ expression inhibited EOC cell migration and induced apoptosis in vitro

We then performed trans-well assay to investigate the role of *PPARγ* in regulation of cell migration in EOC cells. Trans-well assay showed that the migratory rate of EOC cells transfected with *pEGFP-C1-PPARγ* was significantly downregulated compared with mock group (*P*<0.05, **Figure 3C**). In addition, apoptosis analysis revealed that artificially increasing the level of *PPARγ* via transfection also caused a significant increase in apoptosis after 48 h in the OVCAR3 cell lines (*P*<0.05, **Figure 3D**). Taken together, these results indicated that upregulation *PPARγ* may promote the migration and induce apoptosis in OVCAR3 cells.

Discussion

PPAR contains three isoforms, which are *PPARα, PPARβ/δ and PPARγ*. Each of them was encoded by a different gene and displaying a distinct tissue distribution [26]. *PPARγ* is a ligand-activated transcription factor and a member of the nuclear hormone receptor superfamily [27, 28]. It was revealed that *PPARγ* activation stimulates differentiation and apoptosis of various cancer cells such as liposarcoma, prostate carcinoma, colon cancer, pancreatic carcinoma, myeloid leukemia and breast carcinoma [23, 29, 30]. Some evidences have suggested that ligand of *PPARγ* has been linked to apoptosis and inhibition of tumorigenesis. It was reported that combination of *PPARγ* ligand and some agents, such as RXR, histone deacetylase inhibitor, and anti-cancer drug has been shown to efficiently inhibit tumor growth [31-33]. Cho *et al.* revealed that *PPARγ* expression was an independent prognostic factor for overall and gastric cancer-specific mortality in patients with intestinal-type gastric cancer, and *PPARγ* inhibits cell invasion, migration and epithelial-mesenchymal transition through upregulation of galectin-9 in *vitro* and in *vivo* [34].

In this study, we explored the expression of *PPARγ* in EOC, examining its correlation with the biological and clinical features of the cohort.

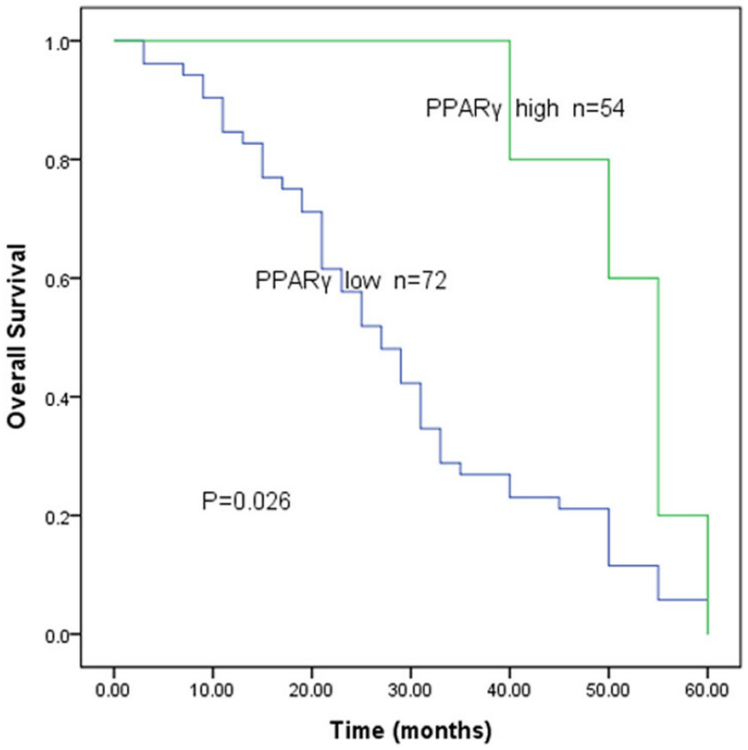

Figure 2. Kaplan-Meier curves for survival time in patients with EOC divided according to *PPARγ* expression: significantly shorter survival time for patients with low *PPARγ* expression than for those with high *PPARγ* expression (*P*<0.05).

Table 2. The multivariate Cox regression analysis of overall survival of cases with ovarian carcinoma

Variables	Multivariate analysis		*P* values
	HR	95% CI	
PPARγ expression	3.073	1.073-8.797	0.037
FIGO stage	1.533	0.867-2.710	0.141
Distant metastasis	1.175	0.670-2.062	0.574
Recurrence	1.314	0.703-2.455	0.393

HR, Hazard ratio; 95% CI, 95% confidence interval.

We found that *PPARγ* was down-regulated in EOC tissues, and down-regulation of *PPARγ* was closely associated with a few clinical features including FIGO stage, distant metastasis and recurrence. However, *PPARγ* expression was not associated with age, tumor size, menopause, and lymph node metastasis. Possati *et al.* had reported that there was a relation between *PPARγ* expression and low incidence of urothelial bladder cancer recurrence [35]. However, Yao *et al.* reported that *PPARγ* was apparent overexpression in human gastric cancer [36]. Therefore, it is necessary to further explore the role of *PPARγ* in EOC.

To better understanding the function of *PPARγ* in EOC, we further performed a series of assays in vitro. Firstly, it was detected the effect of *PPARγ* on cell proliferation using MTT assay. The results showed that aberrant expression of *PPARγ* could significantly suppress the cell proliferation. Furthermore, the transwell migration assays were conducted, and the results demonstrated that aberrant expression of *PPARγ* could inhibit the cell migration ability. Taking together, these results suggested that the regulation of *PPARγ* on cell growth and migration may contribute the development and progression of EOC. Previous studies also investigated the relationship of *PPARγ* with ovarian cancer, for example, Lou *et al.* demonstrated that ligands-activated *PPARγ* suppresses proliferation of ovarian cancer cells though upregulation of *miR-125b* which inhibits proto-oncogene BCL3 expression [37]. Kim *et al.* found that *PPARγ* ligands inhibited cell proliferation and regulated the cell cycle and apoptosis in ovarian cancer cells through p63 and p73 genes [18].

What's more, we also found that the down-regulation of *PPARγ* was significantly associated with worse survival in patients with EOC via Kaplan-Meier methods and log-rank test. Multivariate Cox regression analysis further demonstrated that low expression of *PPARγ* was an independent prognostic indicator for EOC patients. These results indicated that *PPARγ* could be a useful prognostic biomarker to stratify EOC patients into different risk groups and further guide the personalized therapy for EOC patients. Mylona *et al.* revealed *PPARγ* immunopositivity to be associated with a favorable effect on patients with urothelial bladder cancer [38]. Ogino *et al.* reported that patients with *PPARγ*-positive tumors had significantly longer overall survival in Colorectal Cancer patients [39].

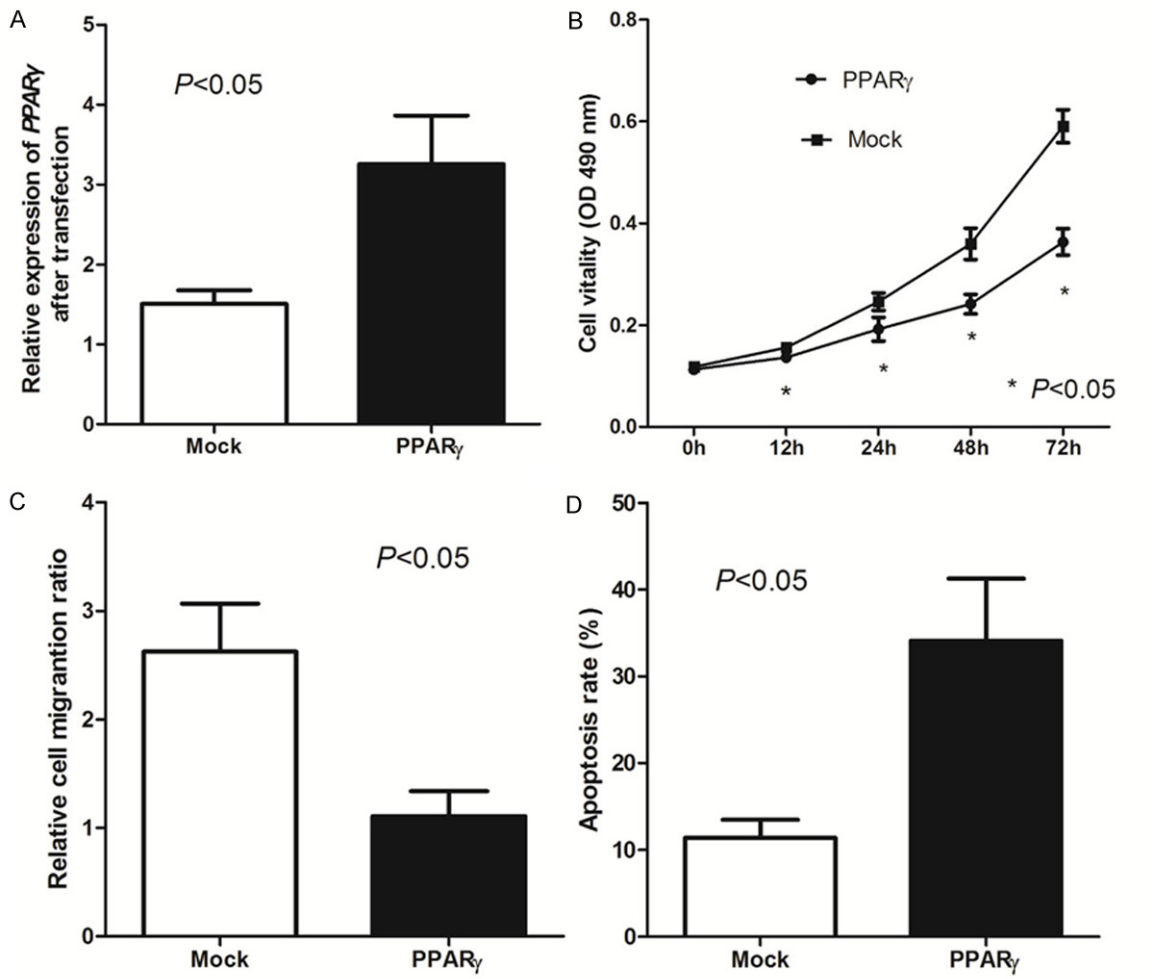

Figure 3. Transfection of *PPARγ* suppresses cell proliferation, migration and apoptosis in *PPARγ* cells. A. The relative expression level of *PPARγ* in OVCAR3 cells transfected with *pEGFP-C1-PPARγ* are significantly increased compared with the mock. B. 24 hours after transfection, MTT assays are conducted to determine the proliferation of OVCAR3 cells. C. Trans-well assay showed that OVCAR3 cells transfected with *pEGFP-C1-PPARγ* displayed significantly lower migration capacity compared with the mock group. D. Cell apoptosis assay showed OVCAR3 cells transfected with *pEGFP-C1-PPARγ* displayed significantly higher apoptosis rate compared with the mock group. Ten areas were randomly selected in each chamber. The number of cells in these areas was counted, and results are expressed as means ± SD for three replicate determination. All data analyzed using Student's t test.

In conclusion, this report found that *PPARγ* was down-regulation in EOC tissues, and associated with poorer survival in patients with EOC. In addition, *PPARγ* was identified as an independent marker for predicting the clinical outcome of EOC patients. Furthermore, aberrant expression of *PPARγ* could suppress cell growth and induced apoptosis. The down-regulation of *PPARγ* plays key roles in EOC progression. These results suggest that *PPARγ* is a promising biomarker and a potential therapeutic target for EOC in future.

Disclosure of conflict of interest

None.

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