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# PPARγ inhibits ovarian cancer cells proliferation through upregulation of miR-125b

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ABSTRACT

miR-125b has essential roles in coordinating tumor proliferation, angiogenesis, invasiveness, metastasis and chemotherapy recurrence. In ovarian cancer miR-125b has been shown to be downregulated and acts as a tumor suppressor by targeting proto-oncogene BCL3. PPARγ, a multiple functional transcription factor, has been reported to have anti-tumor effects through inhibition of proliferation and induction of differentiation and apoptosis by targeting the tumor related genes. However, it is unclear whether miR-125b is regulated by PPARγ in ovarian cancer. In this study, we demonstrated that the miR-125b downregulated in ovarian cancer tissues and cell lines. Ligands-activated PPARγ suppressed proliferation of ovarian cancer cells and this PPARγ-induced growth inhibition is mediated by the upregulation of miR-125b. PPARγ promoted the expression of miR-125b by directly binding to the responsive element in miR-125b gene promoter region. Thus, our results suggest that PPARγ can induce growth suppression of ovarian cancer by upregulating miR-125b which inhibition of proto-oncogene BCL3. These findings will extend our understanding of the function of PPARγ in tumorigenesis and miR-125b may be a therapeutic intervention of ovarian cancer.



## 1. Introduction

MicroRNAs (miRNAs) are short (about 20–25 nucleotides) regulatory noncoding RNAs that can post-transcriptionally regulate the expression of specific target genes and that play important roles in the control of physiological and pathological cellular processes [1,2]. A growing amount of reports have proved that miRNAs have a crucial role in human cancers as it can either act as oncogenes or tumor suppressors that control the cancer onset, growth, and progression [3]. miR-125b is deregulated in many human cancers including lung, gastric, colorectal, ovarian, breast, bladder and hepatocellular cancers [4], and plays a key role in several signaling networks such as IGF-signaling pathway, PI3K/Akt/mTOR pathway, MAPK signaling pathway [5–7]. miR-125b has been shown to be downregulated in ovarian cancer tissues, and acts as a tumor suppressor by targeting BCL3(B-cell CLL/lymphoma 3) and ERBB2/3 (Her2/Her3), which associated with tumor growth and angiogenesis [8,9]. miR-125b regulates so many target genes which related to tumor growth, invasion and metastatic, progression survival and chemotherapy recurrence [10–12], but its own regulation is not well. It has been reported that transcriptional factors CDX2 and STAT3 can modulate miR-125b expression [13,14]. However, there is no concern with nuclear receptor (NR)-mediated regulation of miR-125b.

Peroxisome proliferator-activated receptor gamma (PPARγ), a member of the nuclear receptor superfamily, regulates lipid metabolism, inflammation and cancer progression [15]. Synthetic PPARγ ligands are thiazolidinediones (TZDs), which consist of ciglitazone (CGZ), troglitazone (TGZ), pioglitazone (PGZ) and Rosiglitazone (RGZ). Ligand-activated PPARγ binds to response elements of target genes behaves as transcriptional transrepressors or transactivators [16–18]. PPARγ expression has been shown to be upregulated in ovarian cancer [19,20], making it a potentially important regulator in the cancer progression. PPARγ displays anti-tumor effects through inhibition of proliferation and induction of differentiation and apoptosis by targeting the tumor related genes,

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such as p63, p73, p21, Bax, caspase-3, Bcl-2, c-myc [21–24]. However, it is unclear whether PPARγ can regulate the miR-125b in ovarian cancer.

In this study, we demonstrated that miR-125b downregulated in ovarian cancer tissues and cell lines. Ligands-activated PPARγ suppressed proliferation of ovarian cancer cells and this PPARγ-induced growth inhibition is mediated by the upregulation of miR-125b. PPARγ promoted the expression of miR-125b by directly binding to the responsive element in miR-125b gene promoter region. These results suggest that miR-125b can be regulated by an important transcriptional factor PPARγ and may be a therapeutic intervention of ovarian cancer.

## 2. Materials and methods

### 2.1. Reagents

miR-125b antagomir and negative control (NC) were synthesized by Shanghai GenePharma (Shanghai, China). Ciglitazone (CGZ), Troglitazone (TGZ), and Pioglitazone (PGZ), GW9662 were purchased from Cayman Chemical (Ann Arbor, MI). All-in-One miRNA quantitative reverse transcriptase PCR Detection Kit was purchased from GeneCopoeia (Guangzhou, China). Dual luciferase assay systems were from Promega (Madison, USA). ChIP kit was from Upstate (Lake Placid, USA).

### 2.2. Human tissue samples and cell lines

20 primary serous ovarian carcinomas and 10 normal ovarian tissues were collected by surgical resection. All tissue specimens were snap-frozen in liquid nitrogen. This study was approved by our hospital Ethics Committee in Suining central Hospital.

Ovcar3, CaOv3, Skov3 cells were obtained from American Type Culture Collection. Ovcar3 cells were grown in RPMI-1640 medium with 0.01 mg/ml bovine insulin and 20% fetal bovine serum. CaOV3 cells were cultured in Dulbecco's Modified Medium (DMEM) supplemented with 10% fetal bovine serum. Skov3 cells were maintained in McCoy's 5a medium with 10% fetal bovine serum. The human immortalized ovarian epithelial cells (HIOSE) were generated by transfecting normal ovarian surface epithelial cells with the immortalizing simian virus 40 early genes [25]. HIOSE cells were grown in 199/MDCB 105 (1:1) medium supplemented with 5% fetal bovine serum.

### 2.3. Luciferase reporter vectors construction, transfection and luciferase assays

The promoter of miR-125b was amplified by PCR using CaOV3 cell-derived genomic DNA as template. The PCR product was cloned into pGL3-basic luciferase reporter vector (Promega). The mutations in two PPARγ binding sites were synthesized and cloned into the pGL3-basic by SangonBiotech (Shanghai, China). CaOV3 cells were transfected with reporter luciferase vectors and internal control luciferase vector pRL-TK using Lipofectamine 2000 according to the manufacturer's protocol (Invitrogen). After transfection for 24 h, cells were treated with vehicle DMSO or TGZs (5 μM) for 24 h, then, cells were harvested for luciferase assays using the Dual-Luciferase Assay kit according to the manufacturer's instruction (Promega). All transfection experiments were performed in triplicate and repeated at least three times.

### 2.4. Real-time quantitative reverse transcription PCR

The total RNA was extracted from cells using TRIzol reagent (Invitrogen), and the first-strand cDNA was synthesized by PrimeScript RT Master Mix (TaKaRa). The BCL3 mRNA expression were detected by qRT-PCR using SYBR Green qPCR Master Mix (Promega). The BCL3 primers: forward, 5′-CCATGATGTGCCCCA TGGAA-3′, and reverse, 5′-CTGCTGGAAGAGGTTGACCA -3′. β-Actin was used as an internal control with the pimers5′- GTGA AGGTGACAGCAGTCGGTT-3′ (forward) and 5′-GAAGTGGGGTGG CTT TTAGGA -3′ (reverse). The miR-125b expression was determined using All-in-One™ miRNA qRT-PCR Detection Kit (GeneCopoeia) according to the manufacturer's protocol. The primers for miR-125b: forward: 5′- TCCCTGAGACCCTAACTTGTGA -3′, and the reverse universal primer was supplemented in the detection kit. U6 small nuclear RNA (U6 snRNA) was used as an internal control with the pimers 5′-CGCTTCGGCAGCACATATA CTAA-3′(forward) and 5′-TATGGAACGCTTCACGAATTTGC-3′(reverse).

### 2.5. Western blot analysis

The whole cell proteins were extracted and the protein concentrations were determined by BCA assay (Beyotime, China). Proteins(50 μg) were separated with 12% SDS-PAGE and transferred to polyvinylidene difluoride membranes (Millipore). After incubated with 5% fat-free dry milk in Tris-buffered saline tween-20 (TBST) for 1 h, the membranes were incubated with anti-BCL3 antibody (1:250, Santa Cruz), or GAPDH (1:000, Santa Cruz) at 4°Covernight. And then the membranes were HRP-conjugated anti-goat or anti-rabbit secondary antibodies (1:10,000; Sigma–Aldrich). Signal detection was performed using enhanced chemiluminescence detection reagents (Pierce).

### 2.6. Cell proliferation assay

Cell proliferation was determined by CellTiter 96® AQueous One Solution Reagent (Promega) according to manufacture's instructions. Briefly, $2 \times 10^3$ cells per well were seeded in 96-well plates and cultured for 24 h. Then, the cells were transfected with miR-125b antagomir or NC. After 8 h, cells were treated with DMSO or TGZs (5 μM) for 24 h, then added 20 μl 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.

### 2.7. ChIP assays

ChIP assay was performed using ChIP Assay kit (Upstate) according to the manufacturer's instructions. Briefly, CaOv3 cells were treated with 5 μM TGZ, CGZ, or DMSO for 48 h, then cells were treated with 1% formaldehyde for 10 min at 37 °C to cross-link proteins to DNA. The chromatin was sonicated to shear DNA to an average length between 200 and 1000bp. Subsequently, the chromatin was immunoprecipitated with anti-PPARγ (Santa Cruz) and normal goat IgG (negative control) antibodies. The ChIP DNA was extracted and the purified sample was subjected to PCR amplification with primer pairs spanning the PPRE sequence in the miR-125b promoter region (−344 to −224). Sequences of the primers for PCR were 5′-TGTTTTGTTCTTAACTGCAACG-3′(forward); 5′-CCTAATTGAAATTTTGCTTCCCA-3′(reverse).

### 2.8. Statistical analysis

Data are expressed as mean ± standard deviation (SD). The statistical differences between experimental and control groups were determined by Student's t test. $P < 0.05$ was considered statistically significant.

## 3. Results

### 3.1. miR-125b is down-regulated in ovarian cancer tissues and cells

We detected the expression of miR-125b in 20 ovarian cancer tissues, 10 normal ovarian tissues, and ovarian cancer cell lines by real time PCR. Compared to the normal ovarian tissues, miR-125b was downregulated in ovarian cancer tissues (Fig. 1A). Similarly, the expression of miR-125b was decreased in Ovcar3, CaOv3, Skov3 ovarian cancer cell lines compared to the human immortalized ovarian epithelial cells (HIOSE) (Fig. 1B).

### 3.2. PPARγ upregulates miR-125b, in turn regulating expression of its target gene BCL3

To investigate whether PPARγ is involved in the regulation of miR-125b, CaOv3 cells were treated with PPARγ agonist thiazolidinediones (TZDs), including Ciglitazone (CGZ), Troglitazone (TGZ), and Pioglitazone (PGZ), then, real time PCR and Western blot analysis were performed to detect the expression of miR-125b and its target gene BCL3. As shown in Fig. 2, the PPARγ agonist TZDs increased the expression of mature miR-125b (Fig. 2A) and downregulated its target gene BCL3 (Fig. 2A and B). In order to determine whether this inhibitory effects are PPARγ dependent, we knocked down PPARγ by siRNA, and the expression of miR-125b and its target gene BCL3 were detected by real time PCR and Western blot. Results showed that there was a partial rescue when cells were treated with the PPARγ siRNA (Fig. 2C–E). These results indicated that PPARγ agonist TZDs-induced the upregulation of miR-125b resulted in an increase of inhibitory function of miR-125b, in turn downregulation of its target gene BCL3 expression.

### 3.3. Silence of miR-125b attenuates PPARγ-mediated growth suppression of ovarian cancer cells

To investigate whether PPARγ is involved in the proliferation of ovarian cancer cells, Ovcar3, CaOv3, Skov3 ovarian cancer cells were treated with CGZ, TGZ, and PGZ for 24 h. As shown in Fig. 3A, ovarian cancer cells treatment with these TZDs exhibit a decrease in cell proliferation. Treatment with CGZ resulted in 70% growth inhibition, TGZ caused a 60% decrease, and PGZ reduced proliferation 30%. Thus, PPARγ ligands can inhibit the ovarian cancer cells growth. To clarify whether the antiproliferative effect of PPARγ is mediated by miR-125b, we knocked down miR-125b by miR-125b antagomir. As shown in Fig. 3, PPARγ ligands induce growth inhibition were decreased after treatment of antagomir-125b (Fig. 3B–D). These results suggested that the antiproliferative effect of PPARγ is partially mediated by miR-125b in ovarian cancer cells.

### 3.4. PPARγ promotes the transcription of miR-125b via binding to PPARE in miR-125b gene promoter region

To verify whether PPARγ transcriptional regulate miR-125b expression, we analyzed the promoter region of miR-125b and predicted the potential PPARγ regulatory elements (PPRE) in promoter region of miR-125b (Fig. 4A). We constructed luciferase reporter constructs containing the miR-125b promoter (pGL/pro-miR-125b) and transfected with CaOv3 cells followed by treatment with TZDs. The reporter assay showed that there was a significantly increase in luciferase activity compared with control (Fig. 4B). Then the reporter constructs that contains the mutated PPARγ binding sites were constructed as indicated in Fig. 4C. CaOv3 cells were transfected with PPARγ binding sites mutants respectively (Mut1 and Mut2). The luciferase activity of Mut1 were decreased after treatment with TZDs, by contrast, Mut 2 remained promoting effect on luciferase activity (Fig. 4C). These results showed that PPARγ inhibits the transcription of miR-125b is dependent on the proximal PPARγ binding sites (sites 1), but not site 2.

Furthermore, the ChIP analysis was performed to determine whether PPARγ directly binds to the miR-125b promoter. Chromatin was prepared from cells treated with CGZ,TGZ, or PGZ and were immunoprecipitated with PPARγ antibody or control nonspecific rabbit IgG. The precipitated DNA was subjected to PCR using primers designed to amplify a 120bp fragment containing the PPARγ binding sites 1. As shown in Fig. 4D, an expected 120 bp PCR product were detected from the precipitates by PPARγ antibody. By contrast, the fragment was not amplified from precipitates by control nonspecific rabbit IgG. Together with the above results, it suggested that PPARγ promotes the transcription of miR-125b through binding to proximal sites 1 in miR-125b promoter.

## 4. Discussion

Human miR-125b ubiquitously expresses in brain, ovaries, thyroid gland, spleen, testes, prostate, uterus, placenta and liver, which is misregulated in a variety of cancers [26]. It has been demonstrated that miR-125b is upregulated and plays oncogenic potential roles in colon cancer and hematopoietic tumors, as it induces cell growth and blocks the cell apoptosis [27,28]. In contrast, in other tumors, such as head and neck tumors, gliomas, endometrial tumors, osteosarcomas [4], miR-125b is downregulated and may function as a tumor suppressor. Previous studies identified a

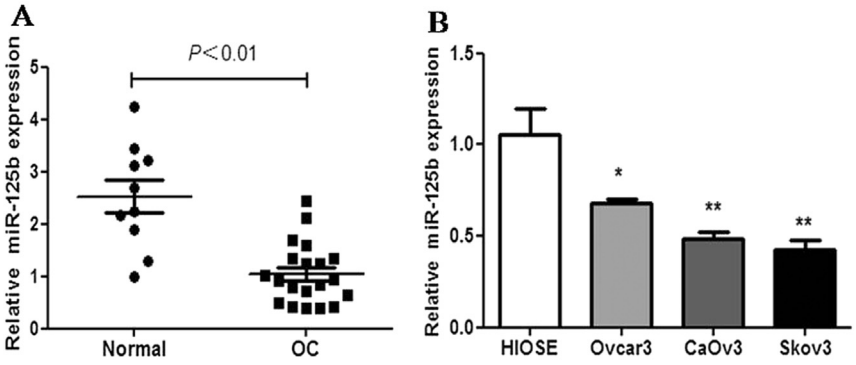


**Fig. 1. Expression of miR-125b in ovarian cancer tissues and cells**. (A) The expression of mature miR-125b in 20 human ovarian cancer tissues and 10 normal ovarian tissues were detected by real time RT-PCR. (B) The relative expression of mature miR-125b in Ovcar3, CaOv3, Skov3 ovarian cancer cell lines and human immortalized ovarian epithelial cells (HIOSE) were determined by real time RT-PCR. miR-125b expression was normalized to U6 snRNA. Data are mean ± SD from triplicate.

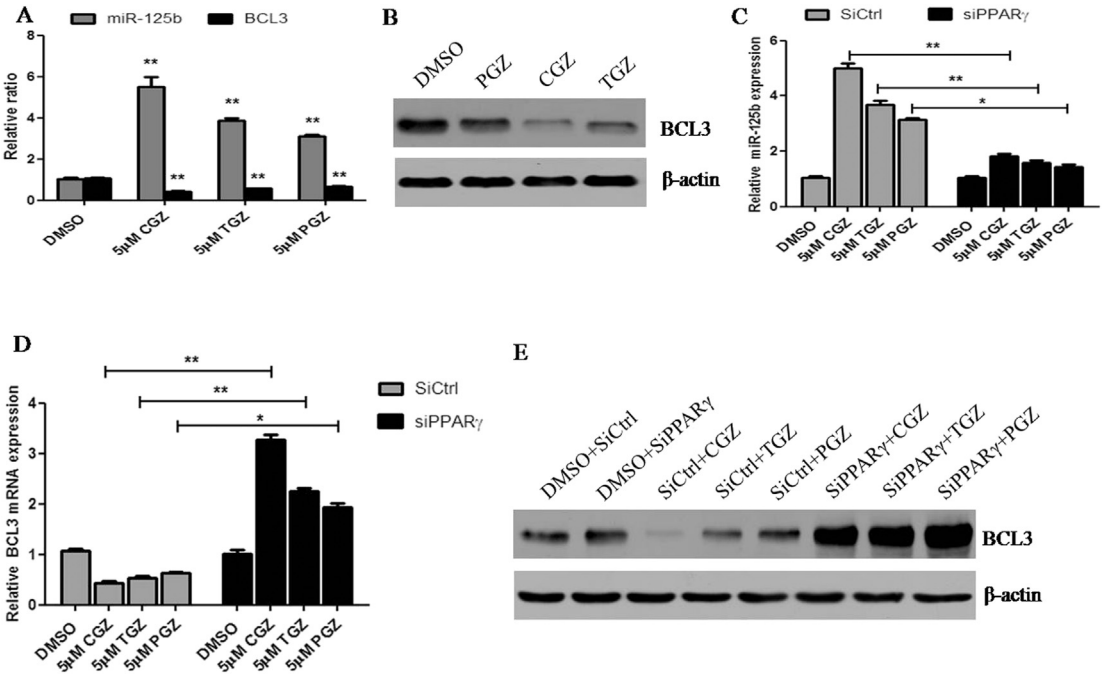


**Fig. 2. PPARγ upregulates expression of miR-125b and downregulats expression of its target gene BCL3**. CaOv3 cells were serum starved for 24 h and treatment with vehicle control (DMSO), or 5 μM CGZ, or TGZ, or PGZ for 24 h, then real time RT-PCR were performed to detected miR-125b and BCL3 mRNA expression(A). The BCL3 protein levels were examined by western blot(B). (C–E) CaOv3 cells were transfected with 10 nM control siRNA or PPARγ siRNA for 24 h, then cells were treated with vehicle DMSO, or 5 μM CGZ, or TGZ, or PGZ for 24 h, the miR-125b (C) and BCL3 mRNA expression (D) were detected by real time RT-PCR, the BCL3 protein levels were examined by western blot(E). BCL3 expression was normalized to β-actin, miR-125b was normalized to U6 snRNA. Data are mean ± SD of three independent experiments. $^{**}P < 0.01$ *vs* DMSO.

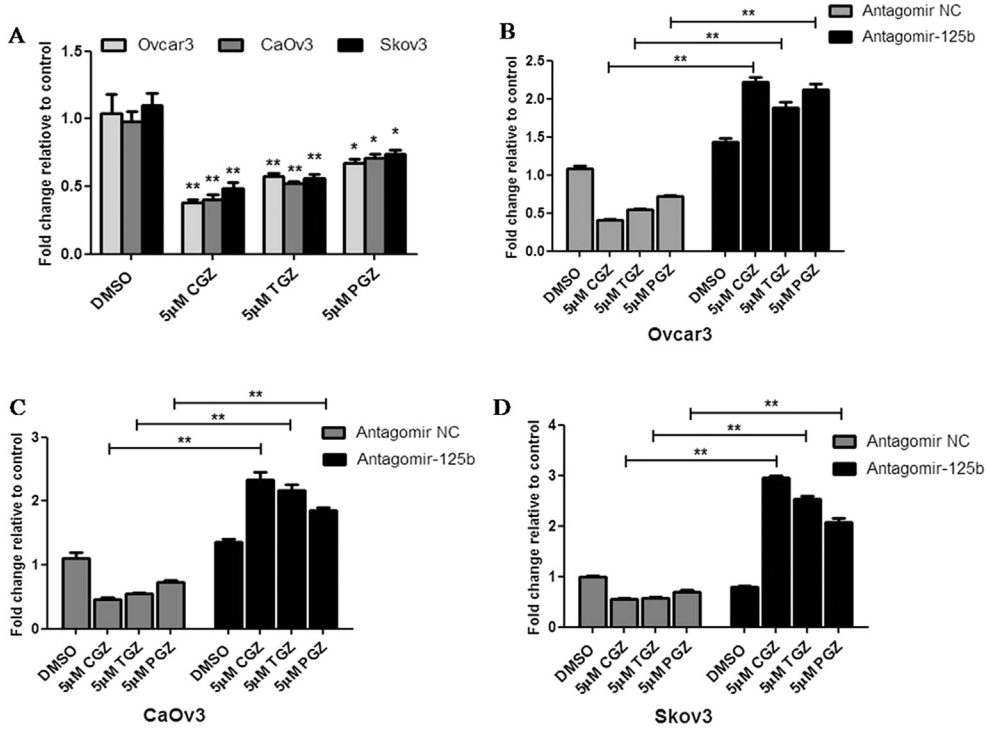


**Fig. 3. Silence of miR-125b attenuates PPARγ-mediated growth suppression of ovarian cancer cells**. (A) Ovcar3, CaOv3 and Skov3 cells were serum starved for 24 h and treatment with vehicle DMSO, or CGZ, or TGZ, or PGZ for 24 h at final concentration 5 μM for additional 24 h. Cells proliferation were assessed with the CellTiter reagent. (B–D) Ovcar3(B), CaOv3(C) and Skov3(D) cells were transfected with antagomir NC, or antagomir-125b, after transfection 24 h, cells were treated with DMSO or 5 μM CGZ, or TGZ, or PGZ for 24 h, then, cells proliferation were examined by CellTiter reagent. Data are the means ± SD for at least three independent experiments. $^{*}P<0.05$, $^{**}P<0.01$ *vs* DMSO.

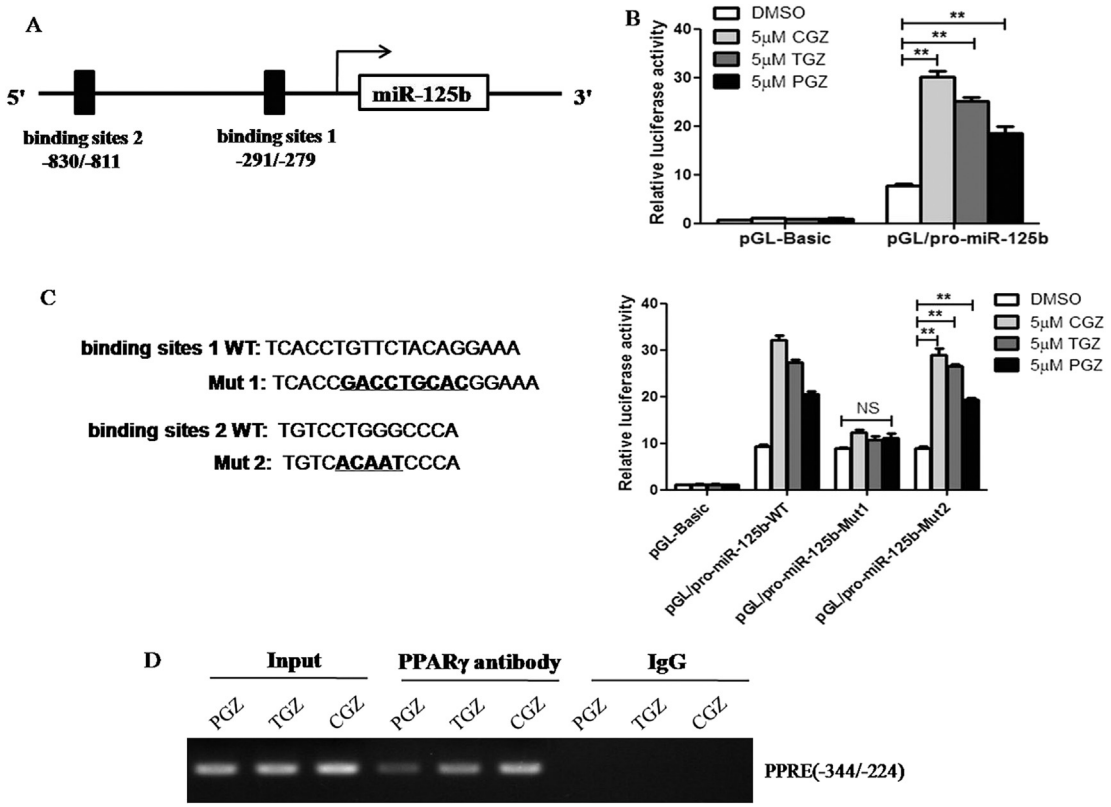


**Fig. 4. PPARγ promotes the transcription of miR-125b via binding to PPARE in miR-125b gene promoter region**. (A) Schematic representation of PPARγ binding elements in promoter of miR-125b. (B) CaOv3 cells were cotransfected with empty vector or luciferase reporter vectors containing the miR-125b promoter, after 24 h, cells were treated with DMSO or5μM CGZ, or TGZ, or PGZ for another 24 h, then the luciferase assays were conducted. (C) Mutant sequences of PPARγ binding sites in miR-125b promoter reporter vector were shown in left panel. Right panel, CaOv3 cells were cotransfected with a empty vector or various luciferase reporter vectors containing the wild type or mutant PPARγ binding sites for 24 h, then cells were treated with DMSO or 5 μM CGZ, or TGZ, or PGZ for another 24 h followed by measurement of luciferase activity. The data were the firefly luciferase activities normalized with the pRL-TK renilla activities. Data are mean ± SD and represented 3 independent experiments carried out in triplicates. *$P$<0.05, **$P$<0.01 *vs* DMSO. (D) Interaction of PPARγ with the putative PPARγ binding sites (sites 1) in the miR-125b promoter region of were examined using a ChIP assay. CaOv3 cells were treated with 5 μM CGZ, TGZ or PGZ for 48 h. DNA isolated from immunoprecipitated material was amplified by PCR using primers that cover PPARγ binding sites (sites 1) in the miR-125b promoter region (−344/−224). One percent of input DNA was used as a positive control for PCR.

number of miRNAs altered in human ovarian cancer, such as miR-141, miR-200abc, miR-199a, miR-140, miR-145, and miR-125b [29]. Consistent with previous report, we showed that miR-125b was down-regulated in ovarian cancer tissues and cell lines. In ovarian cancer, miR-125b acts as a tumor suppressor by targeting BCL3 and ERBB2/3, which associated with tumor growth and angiogenesis. Considering the important role of the miR-125b in ovarian, it is necessary to clarify the transcriptional regulatory mechanism for miR-125b expression. It has been reported that transcriptional factors CDX2 and STAT3 can modulate miR-125b expression [13,14]. However, whether PPARγ, as a multiple functional transcriptional factor, regulates miR-125b is unclear.

Some evidences have suggested that PPARγ has been involved in inhibition of tumorigenesis in several cancers including ovarian cancer [30]. It has been reported that PPARγ activation inhibits cell growth [31] and causes differentiation and apoptosis in a variety of cancer cell types [32]. Activation of PPARγ has been shown to change mitochondrial membrane permeability resulted in the induction of cellular apoptosis [32]. PPARγ activation up-regulated P53 mRNA and protein levels resulted in induction of apoptosis in breast cancer cells MCF-7 [33]. PPARγ agonists also increases the expression of pro-apoptotic proteinsBcl-xl and Mcl-1 Bax and decreases the levels of the antiapoptotic protein Bcl-2 [34,35]. PPARγ agonists has also been reported to inhibit cell growth by inducing a G1 cell cycle arrest, and reduce the expression of the proto-oncogene c-myc [33]. It has been reported that PPARγ is upregulated in ovarian carcinoma, and PPARγ agonists can induce growth suppression and apoptosis of ovarian cancer cells via promoting p63 and p73 expression [21]. In this study, we have shown that PPARγ inhibits ovarian cancer cells proliferation through upregulation of miR-125b that correlated with decreased proto-oncogene BCL3. BCL3 has been found as a proliferative factor, which can combine with NF-kB p50 and p52 isoforms to lead activation of cyclin-D1 promoter resulted in cell proliferation [36]. It has been recently shown that miR-125b targets BCL3 and suppresses ovarian cancer proliferation [8]. Usually, PPARγ regulates target genes by binding the PPARγ response element (PPRE) in the promoter region of target gene and promotes or inhibits the expression of target genes. In this study, we found the potential PPRE in human miR-125b promoter and PPARγ bind to PPRE in the miR-125b promoter to promote the transcription of miR-125b.

In conclusion, we have provided a new insight into the molecular mechanism which PPARγ activation induced growth inhibition in human ovarian cancer cells. we demonstrated that ligands-activated PPARγ suppresses proliferation of ovarian cancer cells though upregulation of miR-125b which inhibits proto-oncogene BCL3 expression. PPARγ promoted the expression of miR-125b by directly binding to the responsive element in miR-125b gene promoter region. These findings will extend our understanding of the function of PPARγ in tumorigenesis and miR-125b may be a therapeutic intervention of ovarian cancer.

## Conflict of interest

None.

## Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.bbrc.2015.04.023.

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