Original Article
Expressions of lysophosphatidic acid receptors in the development of human ovarian carcinoma

Jinge Si1, Yuanyuan Su2, Yifeng Wang3, You-Liang Yan4, Ya-Ling Tang5

1Department of Gynecology and Obstetrics, Zhujiang Hospital of Southern Medical University, Guangzhou 510515, P. R. China; 2Department of Gynecology and Obstetrics, Zhongshan Affiliated Hospital of Sun Yat-Sen University, Zhongshan 528403, P. R. China; 3Department of Gynecology and Obstetrics, Zhujiang Hospital of Southern Medical University, Guangzhou 510515, P. R. China; 4Department of Gynecology, Boai Hospital of Zhongshan, Zhongshan 528403, P. R. China; 5Department of Gynecology, The First Affiliated Hospital of Xiamen University, Xiamen 361003, P. R. China

Received July 3, 2015; Accepted September 5, 2015; Epub October 15, 2015; Published October 30, 2015

Abstract: Aim: To investigate the associations between the expressions of three lysophosphatidic acid (LPA) receptors (LPA1-3) and the development of ovarian carcinoma (OC). Method: Ovarian tissue specimens, including normal ovarian epithelium tissues, benign ovarian tumor tissues and OC tissues were collected from patients who underwent surgical resections between March 2012 and December 2014. Immunohistochemical staining was used to detect LPA receptor expressions in ovarian tissues. Reverse transcription-polymerase chain reaction and Western blotting were used to detect mRNA and protein expression of LPA receptors, respectively. Association analysis between LPA receptors protein expression and clinical pathological characteristics was conducted. The value of LPA2 and LPA3 in discriminating OC was confirmed by receiver-operator characteristic (ROC) curves analysis. Results: The positive expression rates of LPA2 and LPA3 in OC group was obviously higher than normal control and benign groups. The LPA2 and LPA3 mRNA and protein levels in OC group were higher than in normal control and benign groups. LPA2 and LPA3 mRNA expression levels were positively correlated with LPA2 and LPA3 protein expression in OC group. ROC curve analysis revealed that LPA2 yield a specificity of 96.3% and a sensitivity of 97.9%, and LPA3 yield a specificity of 98.5% and a sensitivity of 97.9% for the detection of OC. Conclusion: LPA2 and LPA3 had higher sensitivity and specificity in distinguishing the OC from benign ovarian tumors, which could be potential diagnostic indictors in OC.

Keywords: Ovarian carcinoma, lysophosphatidic acid receptors, pathological stages, pathological grades, pathological types, immunohistochemical staining, reverse transcription-polymerase chain reaction, ROC curve analysis

Introduction

Ovarian carcinoma (OC) is regarded as one of the most lethal tumors of the female reproductive organ and remains the fifth major cause of death related to gynecologic malignancy all around the world [1, 2]. However, the mortality rate in epithelial OC, the most frequent type of OC, is at the highest rate among all types of gynecological tumors [3, 4]. It has been reported that OC affects 22,240 women each year and approximately 14,000 women died of this disease in 2013 according to Surveillance, Epidemiology and End Results data [5]. The prognosis in OC may easily be the poorest among gynecological cancer with overall 5-year survival rate at 45%, steeply dropping down to 20-25% for stages III and IV due to lack of effective therapies for advance-stage OC [6, 7]. Although the etiology of OC is not clearly identified, the development of OC may be caused by the interaction of environmental risk factors and genetic factors [8-10]. Further, greater lifetime ovulations, low parity, nulliparity, nulligravity, infertility, early menarche and late menopause appear to be leading risk factors for OC [11]. Additionally, evidence have showed that breast cancer susceptibility genes significantly enhance the lifetime risk of OC to 27%-44%, and the age and onset of OC is significantly earlier in women carrying breast cancer susceptibility gene mutations [11, 12]. In recent years, various studies have focused on the serum biomarkers which could accurately identify in early
stage of OC to improve the diagnostic accuracy of OC diagnosis [8, 13, 14].

Lysophosphatidic acid (LPA) is a water-soluble phospholipid signaling molecule, which has gained much attention in recent years for its wide-ranging effects in different target tissues [15, 16]. LPA is a multifunctional lipid mediator known for its ability to stimulate cell proliferation, cell migration and survival, smooth muscle cell contraction, platelet aggregation and tumor cell invasion [17, 18]. Evidence has revealed that LPA may be implicated in cell proliferation in various carcinoma cell lines, including OC and prostate cancer cells [19, 20]. LPA is found at relatively low concentrations in plasma but higher concentrations are seen in ascites fluid from OC patients [21]. In addition, LPA also plays an important role in metastatic capacity and reduced susceptibility to apoptosis in OC cell lines treated with cisplatin [7]. Recent studies suggested that LPA is produced by malignant ovarian epithelium and exerts its influence by interacting with G-protein-coupled receptors, including all six LPA receptors (LPA1-6) [13, 22]. Importantly, LPA binding to LPA receptors lead to downstream signaling leading to cell proliferation, differentiation, migration and morphogenesis [14]. These LPA receptors themselves may have different biological mechanisms that are context and tissue dependent, since LPA receptor expression and tissue distribution is diverse [23]. Aberrant expressions of LPA receptors (LPA1, LPA2 and LPA3) have been found in human ovarian tumors, and the LPA1 is mainly expressed in normal ovarian tissues, whereas LPA2 and LPA3 show high expression in OC tissues [24, 25]. The underlying mechanism of the LPA receptors on the development of OC is still unclear; therefore, our study is aimed to investigate the expression levels of LPA (1-3) receptors in ovarian tissues to better understand its clinical significance related to the origin and progression of OC.

Materials and methods

Ethics statement

The study was carried out with the approval of the Institutional Review Board of Southern Medical University. Study subjects were enrolled in this study and tissue samples were collected after obtaining informed written consent. All the study procedures were in line with the Declaration of Helsinki [26].

Study subjects and tissue samples

Human ovarian tissue specimens were collected from patients who underwent surgical resection at the Department of Gynecology and Obstetrics, Zhujiang Hospital of Southern Medical University between March 2012 and December 2014. All specimens were classified by two experienced pathologists based on histopathological evaluation. Fifty samples were confirmed as normal ovarian epithelium tissues obtained from hysteromyoma patients who underwent total hysterectomy with bilateral salpingo-oophorectomy, and were assigned as normal group. The average age of the patients in the normal group was 52.1 ± 7.3 years, ranging from 39 to 65 years. Forty-eight benign ovarian tumor tissues were assigned as benign group. The average age of patients in the benign group was 51.5 ± 10.4 years, ranging from 34 to 72 years. Totally 134 samples were confirmed as epithelial OC tissues and were assigned as OC group. The average age of patients in the OC group was 52.3 ± 9.5 years, ranging from 38 to 69 years. No significant differences were observed on the age among the three groups. The patients with complete clinical data and without any history of receiving radiotherapy and chemotherapy before operation were included in this study. Patients with OC were excluded if they had the following diseases: (1) other malignant neoplasms; (2) pelvic inflammatory diseases; (3) thrombotic diseases; and (4) diabetes, hypertension and coronary heart disease. All specimens were fresh tissue specimens that taken from surgical resections, avoiding the necrotic area and adipose tissues, and all specimens were frozen in liquid nitrogen and stored at -80°C for reserve. Of the 134 OC samples, 68 cases were confirmed as ovarian serous cystadenocarcinoma, 44 cases were ovarian mucinous cystadenocarcinoma, 12 cases were ovarian clear cell carcinoma and 10 cases were endometrioid ovarian carcinoma. On the basis of OC staging classification, 10 samples were in stage I, 34 in stage II, 84 in stage III and 6 in stage IV. Based on OC histological classification, 18 samples were in G1, 50 in G2 and 66 in G3. Both OC staging classification and OC histological classification are based on the International

Federation of Gynaecology and Obstetrics (FIGO) criteria [27].

**Immunohistochemical (IHC) staining**

IHC staining was performed on sections from a selected block of each specimen. Sections were shaking in phosphate buffer saline (PBS) supplemented with 10% bovine serum albumin (BSA). Endogenous peroxides were eliminated with 3% hydrogen peroxide ($H_2O_2$) for 15 min. Sections were blocked with 10% normal goat serum and incubated for 10 min at room temperature. Subsequently, the sections were incubated in rabbit anti-human LPA1 polyclonal antibody (Chemicon), rabbit anti-human LPA2 polyclonal antibody (Chemicon) and rabbit anti-human LPA3 polyclonal antibody (Chemicon) for 1 hour at room temperature, rinsed (three times for 3~5 min each) in PBS. The sections were then incubated with a second biotinylated-conjugated anti-rabbit secondary antibody for 20 min at room temperature, and washed three times in PBS for 3~5 min each. After incubation with streptavidin-horseradish peroxidase (HRP) for 20 min at room temperature and washed three times in PBS for 3~5 min each, 3,3’-diaminobenzidine (DAB) color liquid was added and the sections were observed under the microscope to appropriately terminate the reaction. Finally, the sections were rinsed with tap water, counterstained using hematoxylin, dehydrated by gradient ethanol and mounted with neutral gum. IHC Streptavidin-Peroxidase (SP) kit and DAB kit were purchased from Shanghai-Tian Cheng (Shanghai, China).

The protein expressions of LPAs were observed under the light microscope. Brownish yellow staining of cytoplasm or cytomembrane was recorded positive [28]. One-hundred cells were calculated from each 10 arbitrarily selected high-power fields. The proportion of positive cells was counted in 10 high-power fields and the mean values were calculated. The proportion score described the estimated fraction of positively stained cells (0, no visible reaction; <5%; 1, 6%~25%; 2, 26%~50%; 3, 51%~75%; 4, >75% of positive cells stained).

The intensity score represented the estimated staining intensity (0, no staining; 1, light yellow; 2, yellow; 3, brownish yellow). Evaluation score of the reactive cells was calculated by the intensity score and its proportion score. Based on evaluation score, the expression level of LPA was classified into: 0 points, negative (−); 1~4 points, weakly positive (+); 5~8 points, moderate positive (++); 9~12 points, strongly positive (+++). The “+”, “++”, “+++” were regarded as positive signals with observable increase in staining intensity.

**RT-PCR for LPA (1-3) receptors**

Tissue samples were immersed in Trizol (100 mg/mL) (Sino-American Biotechnology., Ltd.) and then pulverized with a mortar and pestle under ice-bath. Tissue samples were maintained in 1.5 mL EP tube for 5~10 min for the extraction of total RNA. The integrity of RNA was identified by 1.5% agarose gel electrophoresis. The absorbance (OD value) at 260 nm and 280 nm were read with ultraviolet (UV) spectrophotometer for measuring the purity and concentration of total RNA. The transcriptional levels of LPA1, LPA2 and LPA3 were detected by applying reverse transcription polymerase chain reaction (RT-PCR). The β-actin was used as an endogenous reference for LPA1, LPA2 and LPA3. All primers were synthesized at Sangon Biotech Co., Ltd. (Shanghai, China), as listed in Table 1. The total volume of PCR reaction was 30 μL. The amplification conditions of LPA1 and LPA3 were as follows: an initial denaturation at 94°C for 5 min, and 35 cycles of denaturation at 94°C for 15 s, followed by annealing at 57°C for 1 min and extension steps at 72°C for 30 s; and with 1 cycle of

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**Table 1. Primers sequences for LPA1, LPA2, LPA3 and β-actin**

<table>
<thead>
<tr>
<th>Genes</th>
<th>Primers sequences</th>
<th>Product length (bp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPA1</td>
<td>Forward: 5’-ATCGGGAATGATGCTG-3’</td>
<td>342</td>
</tr>
<tr>
<td></td>
<td>Reward: 5’-TCCGTCTAACAAGAGTG-3’</td>
<td></td>
</tr>
<tr>
<td>LPA2</td>
<td>Forward: 5’-GCTACGGAGAACCGCTC-3’</td>
<td>299</td>
</tr>
<tr>
<td></td>
<td>Reward: 5’-CTGGCAGAGGTATGTT-3’</td>
<td></td>
</tr>
<tr>
<td>LPA3</td>
<td>Forward: 5’-ACACCATGAACTAAGG-3’</td>
<td>379</td>
</tr>
<tr>
<td></td>
<td>Reward: 5’-AGGCATCCAGAGTTGAAG-3’</td>
<td></td>
</tr>
<tr>
<td>β-actin</td>
<td>Forward: 5’-ATCGGACACCCCTCAATGAGCTGCG-3’</td>
<td>838</td>
</tr>
<tr>
<td></td>
<td>Reward: 5’-CGTCTAATCCCCTGCTGATCCACATGC-3’</td>
<td></td>
</tr>
</tbody>
</table>

LPA: lysophosphatidic acid; β-actin: endogenous reference.
Figure 1. The expressions of LPA receptors in normal ovarian epithelium tissues, benign ovarian tumor tissues and epithelial ovarian carcinoma tissues by IHC staining (SP × 40). Note: A. Positive expression of LPA1 in benign ovarian tumor tissues; B. Negative expression of LPA1 in epithelial ovarian carcinoma tissues; C. Positive expression of LPA2 in epithelial ovarian carcinoma tissues; D. Negative expression of LPA2 in benign ovarian tumor tissues; E. Positive expression of LPA3 in epithelial ovarian carcinoma tissues; F. Negative expression of LPA3 in benign ovarian tumor tissues. LPA: lysophosphatidic acid; IHC staining: immunohistochemical staining.
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**Table 2. Expression of LPA1, LPA2 and LPA3 protein in normal ovarian epithelium, benign ovarian tumor and epithelial ovarian carcinoma**

<table>
<thead>
<tr>
<th>Groups</th>
<th>LPA1</th>
<th>LPA2</th>
<th>LPA3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control group (n = 50)</td>
<td>49 (98.0%)</td>
<td>16 (32.0%)</td>
<td>20 (40.0%)</td>
</tr>
<tr>
<td>Benign group (n = 48)</td>
<td>46 (95.8%)</td>
<td>15 (31.3%)</td>
<td>20 (41.7%)</td>
</tr>
<tr>
<td>OC group (n = 134)</td>
<td>119 (88.8%)</td>
<td>121 (90.3%)</td>
<td>119 (88.8%)</td>
</tr>
</tbody>
</table>

χ² 5.392 86.240 60.480

<table>
<thead>
<tr>
<th>P</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.068</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

LPA: lysophosphatidic acid; OC: ovarian carcinoma; Note: *compared with the normal control group, P < 0.05; †compared with the benign group, P < 0.05.

Statistics analysis

Data was analyzed using SPSS 19.0 software (SPSS, Inc., Chicago, IL, USA). Quantitative data was presented with mean ± standard deviation (SD). Comparisons between two groups were made using t test and comparison among groups were made by One-Way ANOVA. Categorical data were expressed as numbers and percentages and were analyzed by χ² test or Fisher’s exact probability test. Pearson’s linear correlation analysis was used to test the mRNA and protein expression of LPA. The diagnostic value of LPA1, LPA2 and LPA3 in discriminating OC was confirmed by receiver-operator characteristic (ROC) curves analysis. A P value of < 0.05 was considered as statistically significant.

Results

LPA receptors expression detected by IHC staining

The IHC staining results showed that the cytoplasm or cytomembrane of LPA1, LPA2 and LPA3 protein were brownish yellow staining and recorded positive, and the proportion score and intensity score of the OC cells were significantly higher than those in normal ovarian epithelium cells and benign ovarian tumor cells (Figure 1). There were no significant differences on the positive expression rate of LPA1 among the three groups (both P > 0.05). However, the positive expression rate of LPA2 in OC group was obviously higher than that in normal control group and benign group (both P
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< 0.05). Similar association was also observed on LPA3 protein (both $P < 0.05$). Further, no significant differences were observed on the positive expression rates of LPA2 and LPA3 between the benign group and normal control group ($P > 0.05$) (Table 2).

**mRNA expression of LPA receptors detected by RT-PCR**

The mRNA expression levels of LPA receptors in normal ovarian epithelium tissues, benign ovarian tumor tissues and epithelial OC tissues are shown in Figure 2. RT-PCR results showed that there were no significant differences on LPA1 mRNA expression among the normal control group, benign group and OC group (all $P > 0.05$). However, the mRNA expression of LPA2 in the OC group was significantly higher than that in normal control group and benign group, respectively (both $P < 0.05$). Similar associations were also observed on the LPA3 mRNA expression among the three groups (both $P < 0.05$). Further, no significant differences on LPA2 and LPA3 mRNA expression were observed between normal control group and benign group, respectively (both $P > 0.05$).

**Protein expression of LPA receptors in normal ovarian, benign ovarian tumor and epithelial OC**

LPA receptors protein expression profile in normal ovarian epithelium, benign ovarian tumor and epithelial OC was measured by Western blotting, and the results were illustrated in Figure 3. We found no significant differences in protein expression levels of LPA1 among the...
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Table 3. Associations between LPA1-3 protein expression and clinical pathological characteristics in ovarian carcinoma tissues

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>LPA1</th>
<th>LPA2</th>
<th>LPA3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Levels</td>
<td>P</td>
<td>Levels</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 50</td>
<td>74</td>
<td>0.96 ± 0.16</td>
<td>0.067</td>
<td>0.85 ± 0.12</td>
</tr>
<tr>
<td>&lt; 50</td>
<td>60</td>
<td>1.01 ± 0.15</td>
<td></td>
<td>0.89 ± 0.15</td>
</tr>
<tr>
<td>Pathological type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serous cystadenocarcinoma</td>
<td>68</td>
<td>0.96 ± 0.16</td>
<td>0.225</td>
<td>0.87 ± 0.13</td>
</tr>
<tr>
<td>Mucinous cystadenocarcinoma</td>
<td>44</td>
<td>1.02 ± 0.15</td>
<td></td>
<td>0.85 ± 0.16</td>
</tr>
<tr>
<td>Ovarian clear cell carcinoma</td>
<td>12</td>
<td>1.00 ± 0.17</td>
<td></td>
<td>0.88 ± 0.13</td>
</tr>
<tr>
<td>Endometrioid ovarian carcinoma</td>
<td>10</td>
<td>0.96 ± 0.10</td>
<td></td>
<td>0.94 ± 0.08</td>
</tr>
<tr>
<td>Pathological stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-II</td>
<td>44</td>
<td>0.95 ± 0.16</td>
<td>0.079</td>
<td>0.88 ± 0.13</td>
</tr>
<tr>
<td>III-IV</td>
<td>90</td>
<td>1.00 ± 0.15</td>
<td></td>
<td>0.86 ± 0.14</td>
</tr>
<tr>
<td>Pathological grading</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>18</td>
<td>0.91 ± 0.12</td>
<td>0.095</td>
<td>0.89 ± 0.13</td>
</tr>
<tr>
<td>G2</td>
<td>50</td>
<td>0.98 ± 0.17</td>
<td></td>
<td>0.86 ± 0.13</td>
</tr>
<tr>
<td>G3</td>
<td>66</td>
<td>1.00 ± 0.15</td>
<td></td>
<td>0.87 ± 0.15</td>
</tr>
</tbody>
</table>

LPA: lysophosphatidic acid.

normal control group, benign group and OC group (all \( P > 0.05 \)). Additionally, there were no significant differences on LPA2 and LPA3 protein expression levels in normal ovarian epithelium and benign ovarian tumor (all \( P > 0.05 \)). However, LPA2 and LPA3 protein expression levels were significantly higher in OC group than those in normal control group and benign group, respectively (both \( P < 0.05 \)).

Pearson’s linear correlation analysis results

Pearson’s linear correlation analysis was used to assess the relationship between LPA receptors mRNA expression levels and protein expression levels of LPA receptors among the OC patients. The results revealed that the mRNA expression levels of LPA1, LPA2 and LPA3 were positively associated with the protein expression levels of LPA1, LPA2 and LPA3, respectively (LPA1: \( r = 0.962, P < 0.001 \); LPA2: \( r = 0.953, P < 0.001 \); LPA3: \( r = 0.977, P < 0.001 \)).

Relationship between LPA receptors protein expression and clinical pathological characteristics

Table 3 shows the relationship between LPA receptors expression and clinical pathological characteristics in epithelial OC patients. LPA1 protein expression showed no significant difference on age, pathological type, pathological stage and pathological grading in epithelial OC patients (all \( P > 0.05 \)). Similar associations were also observed on LPA2 and LPA3 protein expression (all \( P > 0.05 \)).

ROC curve analysis of LPA2 and LPA3

ROC curve analysis was performed to assess sensitivity and specificity of the LPA2 and LPA3 for distinguishing the OC from benign ovarian tumors, as shown in Figure 4. The value of area under the curve (AUC) revealed the sensitivity and specificity of the LPA2 and LPA3. For distinguishing OC tissues from benign ovarian tumor tissues, the AUC of LPA2 was 0.992 (95% CI = 0.984-1.000, \( P < 0.001 \)). When the cut-off value was set to the optimal point, 0.625, the specificity was 96.3% and the sensitivity was 97.9%. We also explored whether LPA3 could distinguish patients with OC from patients with benign ovarian tumors. The ROC results demonstrated that the AUC was 0.999 (95% CI = 0.997-1.000, \( P < 0.001 \)). When the cut-off value was set to the optimal point, 0.565, the specificity was 98.5% and the sensitivity was 97.9%.

Discussion

In the present study, we intended to investigate the expression levels of LPA receptors in nor-
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Figure 4. ROC curve analysis using LPA2 and LPA3 for discriminating the ovarian carcinoma from benign ovarian tumors. Note: LPA: lysophosphatidic acid; ROC: receiver-operator characteristic curves.

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mal ovarian epithelium tissues, benign ovarian tumor tissues and epithelial OC tissues to better understand the potential mechanisms of LPA receptors in the development of OC. We found that the mRNA and protein expression of LPA2 and LPA3 in epithelial OC tissues were both significantly higher than those in normal ovarian epithelium tissues and benign ovarian tumor tissues, while no significant differences on LPA1 mRNA and protein expression were observed among the normal control group, benign group and OC group. These results suggested that increased mRNA and protein expression of LPA2 and LPA3 may be implicated in the development of OC. The biological function mediated by LPA in various cancers via LPA receptors is involved in cellular processes such as tumor cell growth, proliferation, differentiation, migration and apoptosis [15, 31]. In addition, an early study has demonstrated that abnormalities in LPA metabolism and function in OC patients may contribute to the initiation and progression of the disease [32]. Pronounced LPA accumulation has been identified in the ascites and blood of patients with OC [33]. LPA can activate OC cells and may inhibit the apoptosis of OC cells, and it can also increase the expression levels of matrix metalloproteases (MMPs) and the urokinase plasminogen activator (uPA), which are crucial mediators of metastasis and invasion of cancer cells [34-36]. Meanwhile, LPA can accelerate the formation of focal adhesion and may enhance the migration of cancer cells via the cell signaling of Rho/ROCK/actomyosin and Ras/MEKK1 [37-39]. Notably, the LPA effects the development of OC is primarily mediated through LPA2 and LPA3 [35, 38].

LPA-LPAR signaling has been reported to promote cell proliferation, migration and invasion suggesting that increased LPA2 and LPA3 expression may pose a significant risk in OC [40]. LPA2 and LPA3 overexpression correlated with the increased tumor size and metastatic potential, correlating with the aggressiveness in ovarian carcinogenesis [38]. Previous studies have shown that increased expression of LPA2 and LPA3 in OC tissues caused overproduction of vascular endothelial growth factor, accelerating angiogenesis and providing microenvironment for tumor cell proliferation, metastasis and invasion [41, 42]. Jeong et al. have indicated that higher mRNA expression of LPA2 was observed in OC cells, and LPA2 may stimulate the expression of COX-2 and cell motility by regulating LPA2/Gi/Src/EGFR/ERK signaling cascade, which may be involved in the progression of OC [43]. Wang and his colleagues have also suggested that the LPA2 and LPA3 expression levels were obviously increased in OC tissues (92.6%) as compared to the benign tissues (45.5%) and normal ovarian tissue (43.8%)
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[44], which was in consistent with our study results. Previous studies have demonstrated that LPA1 may be a negative regulator in the development and progression of OC by inhibiting the cell proliferation and invasion through apoptosis and anoikis in OC [45-47]. However, such associations were not observed in the current study. We suspected that it may be attributed to ethnic differences or sample size. In this regard, further study will need to be confirmed in other populations.

Our findings also suggested that LPA2 and LPA3 had higher sensitivity and specificity in distinguishing the OC from benign ovarian tumors. The ROC curve analysis results showed that the value of AUC of LPA2 was up to 0.992, and when the cut-off value was set to the optimal point, 0.625, the specificity was 96.3% and the sensitivity was 97.9%. Additionally, the AUC of LPA3 was 0.999, and when the cut-off value was set to the optimal point, 0.565, the specificity was 98.5% and the sensitivity was 97.9%. These results implied that the expression of LPA2 and LPA3 could be used as potential diagnostic indicators in the development of OC.

In summary, LPA and its receptors, especially elevated expression levels of LPA2 and LPA3, may play important roles in the initiation and progression of OC. Further, the LPA2 and LPA3 had higher sensitivity and specificity in distinguishing the OC from benign ovarian tumors, which could be potential diagnostic indicators in OC. Further studies with larger sample size are needed to confirm the findings in this study of the strong association of LPA receptors expression with OC risk.

Acknowledgements

We acknowledge the reviewers for their helpful comments on this paper.

Disclosure of conflict of interest

None.

Address correspondence to: Yifeng Wang, Department of Gynecology and Obstetrics, Zhujiang Hospital of Southern Medical University, No. 253 Middle Industrial Avenue, Guangzhou 510515, P. R. China. Tel: +86-020-62782975; E-mail: wangyifeng-0508@163.com

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