LPA3 is a precise therapeutic target and potential biomarker for ovarian cancer

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Abstract
Current studies have demonstrated that significant increased LPA levels to be observed in ascites in patients with ovarian cancer. Although several studies have shown that Lysophosphatidic acid (LPA) related to the progression of ovarian cancer, which LPA receptors (LPARs) and G-coupled protein subtypes mediated in LPA actions have not been clearly elucidated. This study aimed to clarify the roles of LPA and it is subtype-specific LPARs mediating mechanisms in ovarian cancer integrated using bioinformatic analysis and biological experimental approaches. The big data analysis shown that LPA3 was the only differentially expressed LPA receptor among the six LPARs in ovarian cancer and further verified in immunohistochemistry of tissue microarrays. Also found that LPA3 was also highly expressed in ovarian cancer tissue and ovarian cancer cells. Importantly, LPA significantly promoted the proliferation and migration of LPA3-overexpressing ovarian cancer cells, while the LPA-induced actions blocked by Ki16425, a LPAR1/3 antagonist treated, and LPA3-shRNA transfected. In vivo study indicated that the LPA3-overexpressing cell-derived tumors metastasis, tumors volume, and tumors mass were apparently increased in xenografted nude mice. In addition, we also observed that LPA3 was differential high expression in ovarian cancer tissue of the patients. Our studies further confirmed the LPA3/Gi/MAPKs/NF-κB signals were involved in LPA-induced oncogenic actions in ovarian cancer cells. Our findings indicated that the LPA3 might be a novel precise therapeutic target and potential biomarker for ovarian cancer.

Keywords LPA3 · Ovarian cancer · Xenografted mice model · Bioinformatics · Signaling mechanism

Introduction
Lipid signaling molecule LPA regulates multiple cellular functions, such as cell migration, proliferation, and differentiation, as the ligand activates at least six known G protein-coupled LPA receptors (LPA1-6) involved in a variety of physiological and pharmacological processes [1]. Many studies have been reported that LPA accelerates occurrence and development of various cancers, including ovarian cancer, bladder cancer, brain cancer, stomach cancer, kidney cancer, and lung cancer [1–3]. According to the multiple studies reported, it was believed that the role and expression activity of LPA receptor subtypes in different types of tumors showed an obvious tissue specificity. Several research groups including our group reported that LPA1 closely related to lysophosphatidic acid-induced lung cancer, ovarian cancer, and pancreatic cancer progression [4–6]. LPA2 and LPA3 were involved in the regulation of chemoresistance in cancer cells treated with CDDP [7, 8]. LPA was shown to be a biomarker for other gynecological cancers [9], as well as for gastric cancer and lung cancer [5, 10, 11]. LPARs as small molecule targets shown to reflect a potential value in the drugs development of cancer therapy.

Ovarian cancer is a common gynecological malignancy with a high mortality rate [12]. Xu et al. firstly reported that LPA might be a potential biomarker for ovarian cancer due to high pathological concentrations of plasma LPA in ovarian cancer patients [9]. The role of LPARs in ovarian cancer has attracted a lot of attention, such as it was reported that

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LPA-induced metabolic adaptations and tumor aggressiveness mediated by LPA2 in ovarian cancer cells [13]. Subsequently, LPA-induced migration of ovarian cancer cells requires activation of ERM proteins via LPA1 and LPA2 [14]. In addition, MicroRNA-15b targeting for LPAR3 inhibited the PI3K/Akt pathway to alleviate ovarian cancer [15]. The role of LPARs in ovarian cancer has caused widespread concern, but what remains unclear in the current studies is which LPA receptor subtype plays the most critical role in LPA-induced ovarian cancer progression. Therefore, our study will use big data analysis combined with biological methods to clarify the importance of LPA receptor subtypes in the development of ovarian cancer and trying to provide a clear answer to ambiguity in this research field.

Materials and methods

Materials

The A2780 (#CL-0013) and SKOV3 (#CL-0215) ovarian cancer cell lines were obtained from Procell Life Science & Technology Co., Ltd. (Wuhan, China). HO-8910 was from our laboratory. A lentiviral vector was used to overexpress LPA3 in A2780, HO-8910, and SKOV3 cell lines. The reagents that contain LPA (C18:1, #857230P), epidermal growth factor (EGF, #SRP3027), and pertussis toxin (PTX, #P7208) were purchased from Sigma-Aldrich. Other reagents were obtained from Selleck Chemicals, such as PD98059 (#S1177), SP600125 (#S1460), BAY11-7082 (#S2913), AG1478 (#S2728), and SB203580 (#S1076). The anti-p-EGFR (#3777), anti-EGFR (#2085), anti-p-ERK1/2 (#9101), anti-ERK1/2 (#4695), anti-p-JNK (#4671), anti-JNK (#9252), anti-p38 (#8690), anti-p-p38 (#4511), anti-Akt (#4691), anti-p-Akt (#4060), anti-NF-κB (#8242), anti-p-NF-κB (#3033), and anti-α-tubulin (#3873) were obtained from Cell Signaling Technology.

Bioinformatics analysis

The gene expression data of normal ovarian tissue were extracted from genotype-tissue expression (GTEx) database. The gene expression data of ovarian cancer tissue were obtained from the cancer genome atlas (TCGA) database. Then differential gene expression analysis was performed by R Language in ovarian cancer samples and normal ovarian samples.

Cell viability assay

When cells were attached to bottom of 96-well plates, changed to starvation medium for overnight. The cells were stimulated with EGF (20 ng/ml), PD98059 (5 µM), LPA (1 µM), Ki16425 (1 µM), SB203580 (1 µM), PTX (100 ng/ml), BAY11-7082 (1 µM), and SP600125 (5 µM) for 24 h. The activity of cell proliferation was detected by TransDetect TM Cell Counting Kit (CCK, # FC101-01, TransGen Biotech).

Cell migration assay

Cell migration activity was measured by 24-well transwell chambers assay (Transwell, Corning Costar). The cell culture insert with an 8 µM pore size were placed in 24-well plates (lower chamber) containing 500 µl of starvation medium with various stimulants, including LPA (1 µM), Ki16425 (1 µM), EGF (20 ng/ml), SB203580 (1 µM), PD98059 (5 µM), SP600125 (10 µM), BAY11-7082 (1 µM), and AG1478 (1 µM). Then, cells were placed in the cell culture insert with 200 ul of starvation medium (upper chamber). The 24-well plate was returned to the cell incubator for 6 h. The cells were pretreated with PTX (100 ng/ml) for 24 h and then carried out the cell migration assay.

Animal study

The male BALB/c nude mice at 4 weeks of age were purchased from Charles River Laboratories (Beijing, China). Tumor xenograft mice model were implemented by stably overexpressing LPA3 in A2780, HO-8910, and SKOV3 cells. Each BALB/c nude mouse was injected with 4 × 10⁶ control group cells and experimental group cells at its the right and left flanks, respectively. Each kind of ovarian cancer cells were inoculated into 5–6 mice. The tumor size was measured by Vernier caliper weekly until the animals were killed 30 days later. Then the xenograft tumors were subjected to qPCR and immunohistochemistry analyses.

We established a lung metastases model of ovarian cancer in nude mice to evaluate the effects of LPA3 on tumor metastasis. For the intravenous injection, the cancer cells (2 × 10⁶) were injected via the caudal vein to induce lung metastasis. After 30 days, Luciferin (Promega) was injected intraperitoneally into mice at a dose of 150 mg/kg and within 30 min after injection, luciferase imaging was performed. Then the mice were killed and counted the number of lung metastatic nodules which were verified by hematoxylin–eosin (HE) staining.

HE staining and immunohistochemistry

The tumor tissues were dewaxed and stained with an HE staining kit (#G1120, Solarbio, China). The pathological changes were observed under a microscope. The 4-μm-thick sections slides were cut from the paraffin blocks of tumor tissues and then deparaffinized for 15 min after drying. The slides were incubated with primary antibodies for LPA3
(#bs-2882R, BIOSS) and Ki-67 (#bs-23103R, BIOSS) overnight at 4 °C after antigen retrieval and serum closure. The slides were incubated with secondary antibodies for 60 min. The slides were stained with DAB and HE and then detected by a Zeiss microscope.

**The other methods**

The western blot, tissue microarrays, and qPCR were performed as described previously [5, 16]. The cAMP was measured by GloSensor™ cAMP Assay (Promega). Tissue arrays of human ovarian cancer were purchased from Shanghai Outdo Biotech. The F-actin of ovarian cancer cells were stained with phalloidin-Alexa Fluor 555 (#C2203S) obtained from Beyotime.

**Statistical analysis**

All experimental data were performed as mean ± S.E.M. from at least three independent experiments by GraphPad Prism 7.0 software analysis. Differences with \( P < 0.05 \) were considered statistically significant.

**Results**

**LPA3 was the only differential expression gene among LPARs in ovarian cancers**

In this study, we first focused on big data by bioinformatics analysis and then we found that LPA3 was the only differentially expressed LPA receptor among the LPARs in ovarian cancer comparing to the health. According to the volcano map, there were 1236 downregulated genes and 1017 upregulated genes, among which LPA3 expression was upregulated by 12.3 times, but other LPAR family members were not differentially expressed (Fig. 1a). In a statistical analysis of various types of cancers, LPA3 was identified as significant highly expressed gene in ovarian cancer (Fig. 1b).

**LPA3 highly expressed in ovarian cancer specimens and cell lines**

The bioinformatics studies may not accurately reflect the features of clinical ovarian cancer, and we extended the study to detect the expressions of LPA1, LPA2, and LPA3 using immunohistochemistry. 

![Image](image_url)

**Fig. 1** LPA3 higher expressed in ovarian cancer tissues and the cells. 

**a** Volcano map of differentially expressed genes in ovarian cancer samples vs control samples. 

**b** The expression of LPA3 in a variety of types of cancer. 

**c** Comparison of LPA1, LPA2, and LPA3 expression in ovarian cancer tissues \( (n=57) \) and normal tissues \( (n=12) \) using immunohistochemistry. 

**d** The expression of LPA1, LPA2, and LPA3 were determined by immunohistochemistry using the H-scores of ovarian cancer patient tissues and healthy tissues. 

**e** LPARs expression profiles were detected by qPCR in ovarian cancer cell lines.
in patient or normal specimens by immunohistochemistry. LPA1, LPA2, and LPA3 were preferentially expressed in both normal ovarian tissues and ovarian cancer tissues, but the LPA3 expression was significantly upregulated in ovarian cancer specimens compared to normal specimens (Fig. 1c, d). Then, we detected the expression of LPARs in several ovarian cancer cell lines. Our data showed that LPA3 was more highly expressed than other LPARs in both A2780 and SKOV3 cells, but LPA1 expression was as high as LPA3 in HO-8910 cells (Figs. 1e, S1).

**LPA3 involved in LPA-induced ovarian cancer cell proliferation**

We measured the effects of LPA on the proliferative activity of ovarian cancer cells by CCK assay. Three kinds of ovarian cancer cell lines were stimulated with LPA and EGF. Regardless of the differences in the expression profiles of LPARs in A2780, HO-8910, and SKOV3 cells, LPA increased the cell proliferation activity and Ki16425, as an LPA1/3 antagonist, inhibited cell proliferation, indicating that LPA3 played a key role in LPA-induced cell proliferation (Figs. 2a, b, S2a–d). To further demonstrate this point, we constructed LPA3 overexpression and LPA3 knockdown ovarian cancer cell lines to assess the impact on cell proliferation. The results showed that LPA3 overexpression promoted cell proliferation, while LPA3 knockdown decreased the proliferation of ovarian cancer cells (Figs. 2c, d, S2e–h). Although LPA and EGF, as a positive control, could promote cell proliferation, the combination of LPA and EGF had no synergistic effect on the proliferative activity in ovarian cancer cells (Fig. 2a, d).

**LPA3 mediates LPA-induced migration of ovarian cancer cells**

Unlimited self-proliferation and metastasis are the main characteristics of cancer cells. We focused on the cell migration effect of LPA3 in ovarian cancer. Ki16425 remarkably inhibited LPA-induced migration of A2780, SKOV3, and HO-8910 ovarian cancer cells (Figs. 2e, S2i, j). LPA3 knockdown also inhibited cell motility in A2780, SKOV3, and HO-8910 ovarian cancer cells (Figs. 2f, S2k, l). LPA3 overexpression significantly increased the cell migration activity compared with that of the control group in A2780, HO-8910, and SKOV3 cells (Figs. 2g, S2m, n).

**LPA3 exerted in vivo tumorigenesis and metastasis**

The experiments in nude mouse model of human ovarian cancer were used to evaluate the in vivo effect of LPA3 on tumorigenesis and metastasis in ovarian cancer. The
overexpression of LPA3 substantially accelerated the tumor growth rate compared to that in the control group, regardless of the ovarian cancer cell type. The mean of tumors volume and mass in the experimental group were remarkably larger than those in the control (Figs. 3a–c, S3). Higher expression of LPA3 and Ki-67 was measured in the LPA3-overexpressing cancer cells derived tumor tissues and also indicated that LPA3 enhanced the cell proliferation ability (Fig. 3d–f). We assessed the effect of LPA3 on tumor metastasis in vivo and we further injected A2780-LPA3 overexpressing or control cells into mice via the tail vein. The mice were anesthetized after 30 days, given an intraperitoneal injection of luciferin, and imaged using an in vivo imaging system (IVIS). The lung tissues of nude mice stained with HE showed the morphological characteristics of metastatic tumor. The results further

![Image]

**Fig. 3** LPA stimulates tumor growth and metastasis via LPA3 in vivo. a Image of tumors in the xenografted mice model: LPA3-overexpressing ovarian cancer cells and controls were injected subcutaneously into the left and right flanks of mice (n = 5). b The tumors were dissected and weighed at on day 30. c The tumor volume was monitored and measured once a week. d Histological morphology analysis of tumor tissue sections from A2780 tumor-bearing mice stained with HE. Immunostaining of tumor tissue sections from A2780 tumor-bearing mice and antibodies against LPA3 and Ki-67 (400 ×). e and f Image-based quantification of LPA3 and Ki-67. g Images of nude mice with a lung metastasis (n = 4). h Quantification of fluorescence intensity. i The photos of HE-stained lung sections. j Statistical analysis of lung metastatic nodules.
appeared that the fluorescence and the number of pulmonary nodules increased clearly with LPA3 overexpression (Fig. 3g–j).

**Signal mechanism for LPA3-mediated actions**

The inhibitor specific to G protein and the determination of cAMP response were used to clarify the type of G protein coupled by LPA3 in ovarian cancer cells. Our results indicated that LPA via LPA3 inhibited cAMP accumulation in A2780 cells and PTX, a specific Gi protein inhibitor, blocked LPA-induced proliferation and migration of the cells (Fig. 4a–c). The PTX suppressed LPA/LPA3-mediated phosphorylation of p38, JNK, AKT, and ERK1/2, while no significant above effects were observed in the cells treated by SQ (SQ22536, an inhibitor of adenylate cyclase) (Fig. S4a, b). These results seem to show that LPA stimulated proliferation and migration mediated by LPA3 coupled with Gi protein in A2780 cells.

We also examined whether LPA3 transactivates epidermal growth factor receptor (EGFR) in ovarian cancer cells. The results showed that no synergistic effect was observed between LPA3 and EGFR on ovarian cancer cell migration and proliferation (Figs. 4d, e, S2o). Transactivation of EGFR by LPA3 was also not detected in the cell function assay and the measurement of EGFR phosphorylation level, these results indicated that LPA3 did not cause EGFR transactivation in ovarian cancer cells (Fig. 4g).

Mitogen-activated protein kinase (MAPK) cascades are related to cancer, and we examined LPA3-mediated MAPK activation in A2780 cells. The phosphorylation of JNK, p38 MAPK, and ERK1/2 was increased in LPA3 overexpression group than those in the control (Fig. 4g). We further used inhibitors specific to MAPK in cell proliferation and migration assay. SB203580 (a p38 inhibitor) markedly suppressed cell migration and proliferation of LPA3-overexpressing cells, and PD98059 (an ERK1/2 inhibitor) significantly attenuated cell migration of the LPA3-overexpressing cells (Fig. 4b, c). However, SP600125 (a JNK inhibitor) hardly affected cell proliferation and migration of the LPA3-overexpressing cells (Fig. 4b, c).

The signaling pathway of Akt and Nuclear factor kappa B (NF-κB) has been linked to ovarian cancer [17, 18]. Importantly, we found that the phosphorylation of Akt and NF-κB was remarkably increased in the LPA3 overexpression group compared with the control (Fig. 4g). While BAY11-7082, a specific inhibitor for NF-κB, abolished LPA3-mediated migration and proliferation of ovarian cancer cells, indicating that NF-κB was involved in LPA3-mediated cell migration and proliferation in ovarian cancer cells (Fig. 4b, c). The F-actin of cellular scaffold was constructed by staining with phalloidin-Alexa Fluor 555 and DAPI stained the nucleus blue. Under laser confocal microscope, the F-actin showed red filamentous. LPA3 induced a typical bunched tension filament structure and the number of F-actin was significantly increased to compare with the control, indicating LPA3-mediated signal influenced cell mobility (Fig. 4f).

**Discussion**

Ovarian cancer remains a common gynecological malignancy with a high mortality rate worldwide since it was reported by Krukenberg in 1896 [12, 19]. Since the fact that LPA accumulates in ovarian cancer ascites and increased plasma LPA concentration in ovarian cancer patients had been reported, a lot of research focused on the relationship between the roles of LPA/LPARs and ovarian cancer progression. Park et al. reported that LPA via LPA1 and LPA2 induced the migration of ovarian cancer cells [14]. Hadil et al. demonstrated that LPA2 and LPA3 were involved in tumor progression through the AKT and ERK signaling pathways, whereas LPA6 mediated the activation of AKT, affecting cell migration [20]. However, the expression activity of the LPA receptor subtype and its prevalence in ovarian cancer were not clearly demonstrated at the present stage, and which LPA receptor subtypes played a key role in LPA-enhanced ovarian cancer progression is still unclear. Therefore, the purpose of our study is to clarify these ambiguities, in order to uncover which LPA receptor subtype is the most important potential therapeutic target for ovarian cancer. In this study, we analyzed both the TCGA and the GTEx database and found that LPA3 was the only differentially expressed gene among LPARs comparing patients with ovarian cancer to healthy controls. The expression of LPA3 increased by 12.3-fold in ovarian cancer samples compared with the control samples, while other LPARs were not. We confirmed that results of LPA1-3 expression in ovarian tumor specimens by immunohistochemistry analysis were consistent with those of the bioinformatics analysis. Our findings suggested that LPA enhanced the proliferation and migration response in several ovarian cancer cell lines as well as in LPA3 overexpressing ovarian cancer cell. Conversely, the cell migration and proliferation attenuated by LPA3 knockdown and Ki16425 treatment in ovarian cancer cells. In animal study, LPA3 overexpression markedly increased tumor mass and volume and promoted tumor metastasis in vivo, indicating LPA3 exists a carcinogenicity. Both in vitro and in vivo data suggested that LPA3 plays a key role in LPA-induced actions in ovarian cancer.

One of the challenges in targeting LPARs is the complex array of G proteins with which they can couple, resulting in multifaceted outcomes. There are different types of G proteins, including Gq, G13, and Gi couples...
Fig. 4 Signaling pathways involved in proliferation and migration induced by LPA in A2780 cells. a The LPA3-overexpressing A2780 cells were stimulated by 1 μM LPA and 1 μM Forskolin, then, luminescence intensity was detected by multifunctional microplate reader. b LPA3 overexpression A2780 cells were stimulated by 1 μM LPA and 20 ng/mL EGF at the conditions of present with 5 μM PD98059, 1 μM SB203580, 5 μM SP600125, 1 μM BAY11-7082, and 100 ng/ml PTX for 24 h. The cell proliferation was detected by the CCK assay. c The LPA3-overexpressing cells were stimulated by 1 μM LPA or 20 ng/ml EGF for 24 h after pretreatment with different inhibitors, namely, PTX, PD98059, SB203580, SP600125, and BAY11-7082. Then, Transwell assay was used to monitor the migration of ovarian cancer cells. d LPA3-overexpressing A2780 cells were treated with 1 μM LPA, 1 μM AG1478, and 20 ng/ml EGF for 24 h and then cell proliferation was performed by CCK assay. e A2780-LPA3 cells were stimulated by 1 μM LPA, 1 μM AG1478, and 20 ng/mL EGF for 6 h and then cell migration was measured by Transwell assay. f Effect of LPA3 on the cytoskeleton rearrangement in A2780 cells, F-actin and nucleus were stained with phalloidin-Alexa Fluor 555 and DAPI (100×). g LPA3-overexpressing A2780 cells were stimulated with 1 μM LPA and 20 ng/ml EGF for 15 min, then the effects of LPA on MAPKs, AKT, and NF-κB phosphorylation were measured by western blotting. h Signaling mechanism of LPA3 mediated tumorigenic actions in ovarian cancer cells.
with LPA3 receptor, depending on the cell types and the environment condition. Excitingly, we found that LPA via LPA3 induced an inhibition of cAMP accumulation in A2780 cells. LPA3-mediated proliferation and migration in A2780 cells were blocked by PTX pretreatment, indicating that LPA3 coupled with Gi protein in the cells. MAPK, AKT, and NF-κB are closely related to the cell proliferation, migration, survival, protein synthesis, glucose metabolism, and so on. In the study, we observed that LPA increased the phosphorylation of MAPK, NF-κB, and AKT proteins, and LPA-induced effects were strongly inhibited by inhibitors for these proteins, indicating that MAPK, Akt, and NF-κB could be involved in LPA3-mediated migration and proliferation in ovarian cancer cells. Activated NF-κB regulates cell proliferation and migration through cyclin and matrix metalloproteinase-mediated pathways, also regulates cell proliferation, survival and migration by stimulating TNF-α, IL-6, IL-8, IL-1, and other inflammatory factors secretion, and then secondary regulated by these factors in the pro-inflammatory cytokines receptor-mediated manner [21, 22]. Our results also showed that LPA/LPA3-mediating signal accelerated the expression levels of four inflammatory cytokines IL1B, IL-6, IL-8, and TNFα in A2780 cells (Fig. S4c-g). Therefore, we hold the opinion that the main way to promote progression of ovarian cancer in response to LPA/LPA3-induced actions is probably by stimulating the expression of pro-inflammatory cytokines.

One hallmark of cancer is the uncontrolled proliferation of cancer cells. Our results indicated that the LPA/LPA3/Gi/p38 or Akt/NF-κB signaling pathway is involved in the proliferation in response to LPA in ovarian cancer cells (Fig. 4h). Metastasis, migration, and invasion are essential processes during cancer metastatic progression, which is responsible for approximately 90% of cancer-associated death and is a major problem in cancer treatment [23, 24]. We also found that the LPA/LPA3/Gi/ERK1/2, p38, or Akt/NF-κB signaling was involved in ovarian cancer cells migration (Fig. 4h). Therefore, we propose LPA3 antagonists as potential therapeutic drugs for ovarian cancer.

Conclusion

In conclusion, based on biological approaches combined with cancer database analysis, we clearly summarized and clarified the key role of LPA3 in LPA-induced ovarian cancer progression. Our findings suggested that LPA3 antagonists may be a potential therapeutic drug for the ovarian cancer.

Supplementary Information  The online version contains supplementary material available at https://doi.org/10.1007/s12032-021-01616-5.

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Author contributions  AD and PZ contributed to design the study. PZ, QY, AL, RL, and YY performed the experiment and collected data. YW performed the animal experiments. PZ and HS analyzed the data and wrote the manuscript. AD revised manuscript critically for important intellectual content and final approval of the version submitted for publication. All the authors approved the final manuscript.

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Data availability  All data included in this study are available upon request by contact with the corresponding author.

Code availability  Not applicable.

Declarations

Conflict of interest  The authors report no conflict of interest for this work.

Ethical approval  All experiments used in this study were performed with ethical standards that the Declaration of Helsinki and national and international guidelines. This investigation was reviewed and approved by the Institutional Animal Care and Use Committee of Inner Mongolia University (Approval Number 20200001).

Consent to participate  Not applicable.

Consent for publication  Not applicable.

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