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Lysophosphatidic Acid- A Target in Ovarian and Endometrial Cancer Therapy

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Abstract

Lysophosphatidic acid (LPA), one of the simplest and most potent lysophospholipids exerting many physiological and pathological actions on various cell types, plays also an essential role in tumorigenesis and cancer metastasis. Overexpression of LPA and its receptors is a common phenomenon in metastatic carcinomas that can be used in new diagnostics strategies. Both, in the ovarian and endometrial cancer cells, LPA activates various signal transduction pathways, leading to the increased proliferation and metastatic abilities of the cells. In this review we would like to prove that development of potential treatment strategies by targeting LPA has a great promise in therapeutics.

Keywords: Lysophosphatidic acid; Lysophosphatidic acid receptors; Phosphatidic acid; Phospholipids

Abbreviations LPA: Lysophosphatidic Acid; Lpars: Lysophosphatidic Acid Receptors; PA: Phosphatidic Acid; Pls: Phospholipids; PLD: Phospholipase D; ATX: Autotoxin; PLA: Phospholipase A; Lpls: Lysophospholipids; Spla2-Secretory Phospholipase A2; PS-PLA1: Phosphatidylserine-specific Phospholipase A1; LCAT: Lecithin-Cholesterol Acyltransferase; FIGO: Federation of Gynecology and Obstetrics; VEGF: Vascular Endothelial Growth Factor; HIF-1α: Hypoxia Inducibe Factor-1α; IGF2: Insulin-like Growth Factor-2; hTR: RNA Component; hTERT: Human Telomerase Reverse Transcriptase Activity; HREs: Hypoxia-responsive Elements; MMPs: Matrix Metalloproteinases

Introduction

The present article focuses particularly on one of the simplest and most potent lysophospholipids-lysophosphatidic acid (LPA) and summarizes recent knowledge on the biological role of LPA signaling via LPA receptors (LPARs) in the pathogenesis of ovarian and endometrial cancer. We would also like to search for the evidence to present LPA as target molecule for the establishment of novel chemoprevention agents in clinical cancer approaches.

Lysophosphatidic acid production

Lysophosphatidic acid is a simple phospholipid that consists of a phosphate, a glycerol and a fatty acid. Initially the first studies revealed LPA effects on blood pressure, uterine smooth muscle contraction and platelet aggregation [1-3]. Subsequently, different studies revealed the effects of LPA on many other physiological and pathological actions in various cell types, such as: cell proliferation and differentiation [4], cytoskeletal rearrangement [5] or cell-to-cell interactions [6]. Finally, it has been proven that LPA is implicated in the pathogenesis of various diseases in the human including carcinogenic cell invasion and tumorigenesis [7].

In the human body LPA can be found both intra and extracellular. It was detected in many various biological fluids such as serum and plasma [8,9], tears [10], ascites [11], seminal plasma [12] and follicular fluid [13]. Moreover, it can also be produced in various cell types like: endometrial cells [14], ovarian cells [14-16], mast cells [17], erythrocytes [18] and neurons [19].

In the human body, two general pathways of LPA production have been demonstrated. In the first pathway phosphatidic acid (PA) is produced from phospholipids (PLs) by phospholipase D (PLD), also called autotaxin (ATX) or from diacylglycerol by diacylglycerol kinase and consequently there is deacylation of PA to LPA by phospholipase (PLA)-type enzymes [20]. In the second pathway, PLs are first converted to lysophospholipids (LPLs) by the action of secretory (sPLA2), PS-PLA1, and lecithin-cholesterol acyltransferase (LCAT), and then the LPL is converted to LPA by ATX [8]. The first pathway is characteristic for intracellular LPA production while the second for serum and plasma. These two ways of LPA synthesis reflect possible levels of regulation-or deregulation in the organism being especially important at such pathological status as cancer [7]. Moreover, LPA-dependent different signaling pathways have clear therapeutic repercussions since pharmaceutical drugs targeting certain enzymes differ from those targeting other LPA biosynthetic pathways [21,22].

G protein coupled receptor-mediated LPA signaling

In mammals, LPA interacts with G protein-coupled transmembrane receptors. So far, at least six types of LPA receptors (LPAR) have been identified, such as LPAR1/EDG2, LPAR2/EDG4, LPAR3/EDG7, LPAR4/P2Y9/GPR23, LPAR5/GPR92 and LPAR6/P2Y5 as well as newly identified GPR87 [23]. These LPARs are expressed in various organs and cells [20]. LPA signaling via various LPARs leads to a variety of cellular responses such as for example cell growth, migration, differentiation, morphogenesis and protection from apoptosis [24]. In recent studies, it has been demonstrated that LPA receptors are new candidates for therapeutic targets in cancer therapy [25]. There is also much evidence in the literature describing

overexpression of one or more of LPARs in certain types of cancers. However, most cancers overexpress multiple subtypes of LPA receptors (LPARs) [26]. Especifically, LPAR1 has been shown to be a regulator of cancer cell motility and metastasis [27,28]. Ovarian cancers predominantly express LPAR2 which are likely to play an important role their aggressiveness [29]. LPAR3 is the dominant receptor subtype in some human melanomas and might be inhibitory to their growth and viability [30]. On the other hand, LPAR4, LPAR5 and LPAR6 are also expressed in the human ovary but at relatively low levels [31].

The influence of LPA on the reproductive system function of the female has been examined and described for about 30 years. Since the first reports published by Jarvis et al. [32] in women, the involvement of LPA signaling in the female reproductive organ disfunction clearly point at the possible development of the future therapeutic strategies. The present article focuses particularly on LPA as the potential (Figure 1).

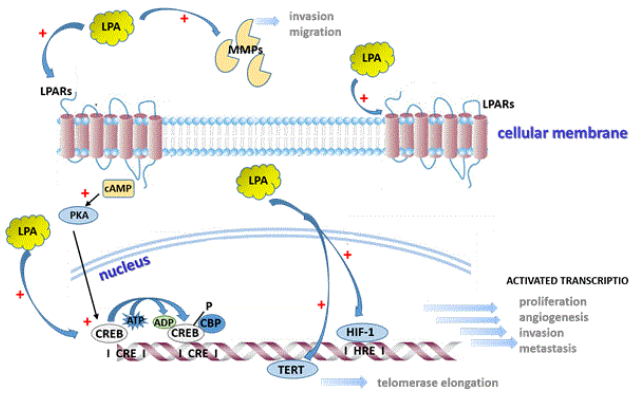

Figure 1: Lysophosphatidic acid as a molecular target in ovarian and endometrial cancer therapy (the abbreviations on the figure stand for: LPA: Lysophosphatidic Acid; LPARs: Different Lysophosphatidic Acid Receptors; MMPs: Matrix Metalloproteinases; cAMP: Cyclic Adenosine Monophosphate; ATP: Adenosine Triphosphate; ADP: Adenosine Diphosphate; PKA: Protein Kinase A; CREB: cAMP Response Element-binding protein; CRE: cAMP Response Element; TERT: Telomerase Reverse Transcriptase; HIF-1: Hypoxia Inducibe Factor-1; HRE: Hypoxia-responsive Element).

Lysophosphatidic acid as a therapeutic target in ovarian cancer

These days ovarian cancer causes more mortalities than any other gynecological cancer distinctive for female population worldwide. This type of cancer occurs mostly after menopause when the ovaries have limited physiological role therefore impaired ovarian function rarely causes any symptoms. Moreover, deep in the pelvis anatomical location of the ovaries precludes many symptoms of this neoplasm unless the tumor reaches large size or is disseminated towards other organs. Taking above into consideration, there are a lot of difficulties in detection of ovarian cancer in its early stage [33]. Due to this fact, ovarian cancer is usually diagnosed at its advanced stage when the survival rates are poor. Almost 90% of women are diagnosed with metastatic disease in the pelvis or abdomen and for these patients 5-year survival rates are lower than 30%. In contrast, in patients diagnosed with early stage of ovarian cancer confined only to the ovaries, the 5-year survival rate exceeds even 90% [34]. The symptoms of ovarian cancer are pelvic or abdominal pain, urinary frequency or urgency, increased abdominal size or bloating and difficulty in ingestion [35,36].

Ovarian tumor stage is determined according to the International Federation of Gynecology and Obstetrics (FIGO) staging system. There are four stages of ovarian cancer. In the I stage, the tumor is confined to ovaries or fallopian tubes. In the II stage, the tumor involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer. In the III stage, the tumor involves one or both ovaries or fallopian tubes or primary peritoneal cancer with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes. In the most advanced stage IV distant metastases excluding peritoneal metastases occur [37].

Due to the fact, that there are a lot of difficulties in detection of ovarian cancer, it is essential to develop a specific and sensitive method for its early detection and treatment. On the other hand, this type of cancer is the most thoroughly studied with respect to LPA signaling in carcinogenesis. It is known that LPA is produced by ovarian cancer cells and acts as the ovarian cancer activating factor [14,38,39]. It was found that LPA levels in the serum samples from ovarian cancer patients were much higher than in the serum samples from the group of healthy patients [40]. However, there are also reports that there was no difference in LPA levels between malignant and benign ovarian cancer tumors [33]. Increased levels of LPA were also found in ascites of ovarian cancer patients and in the corresponding plasma samples [38,41-43].

Taking into consideration the ethiopathology of ovarian cancer, many studies suggested that LPA played very important role in the progression and pathogenesis of ovarian cancer [39,44-49]. In the aspect of cancer progression, Goldsmith et al. [47] documented that LPA stimulated the proliferation of ovarian cancer cells via the gep proto-oncogene $G\alpha_{12}$, which is the most potent α subunit in promoting cell proliferation and neoplastic transformation [47,50]. LPA stimulated the potent activation of CREB via the proto-oncogene $G\alpha_{12}$ by stimulating the phosphorylation of Ser133 of cAMP response element-binding protein (CREB), leading to activation of CREB, which has been implicated in ovarian cancer cell proliferation [51]. Linnerth et al. [51] also demonstrated that LPA activated CREB very rapidly – the activation was observed 3 minutes after LPA treatment. Moreover, the phosphorylation of CREB was stimulated by the expression of the constitutively activated mutation of $G\alpha_{12}$ even in the absence of LPA, whereas silencing $G\alpha_{12}$ abrogated LPA-activated stimulation of CREB. Therefore, LPA-mediated activation of CREB via $G\alpha_{12}$ was through the cAMP-independent mechanism in which Ras-ERK-dependent signalling pathway was involved [51]. Also, the expression of the dominant negative S133A mutant CREB led to the attenuation of the proliferation of ovarian cancer cells stimulated by LPA [51]. It proves that LPA-$G\alpha_{12}$ signalling axis is involved in ovarian cancer cell proliferation. There is the unique $G\alpha_{12}$-dependent mechanism through which LPA signalling converges on CREB to stimulate the proliferation of ovarian cancer cells [49].

There are continuous efforts in the literature to establish whether different cellular effects on cell proliferation, motility and invasion in cancer cells depend on the type of LPA receptor. Many studies documented the overexpression of LPAR2 and LPAR3 in ovarian cancer cell lines in comparison with normal ovarian epithelial cells

[29,39,52]. The elevated expression of LPAR2 and LPAR3 also stimulated the migration and invasion of ovarian cancer cells [53]. What is more, LPA promoted angiogenesis in ovarian tumors via the stimulation of vascular endothelial growth factor (VEGF) expression [54]. Goetzl et al. [29] and Hu et al. [54] demonstrated that LPA induced mRNA and protein expression of VEGF, indicating mainly LPAR2 involvement in this process. Moreover, Fujita et al. [55] documented the correlation between the LPAR2 and LPAR3 expression levels and the induction of VEGF expression in ovarian cancer cells. Moreover, the study of Yu et al. [53] proved that the knockdown of LPAR2 and LPAR3 led to the suppression of the production of VEGF in ovarian cancer cells. Lee et al. [56] reported that LPA induced VEGF expression through the activation of Hypoxia Inducibe Factor-1α (HIF-1α), which is known to play the central role in tumor progression and angiogenesis [57-59]. Through binding to the hypoxia responsive elements within the target gene, HIF-1 activates transcription of various hypoxia-inducibel genes, such as angiogenic-VEGF or proliferation/survival factors-insuline-like growth factor-2 (IGF2) [60]. Therefore LPA-induced HIF-1α activation was probably regulated by translational regulation, not by protein stabilisation [56].

Other factor playing the crucial role in tumorigenesis is telomerase. Telomerase is an RNA-dependent DNA polymerase, synthesizing telomeric DNA [61]. It contains two components: the RNA component (hTR) that is the template for telomeric DNA synthesis and the catalytic protein with the human telomerase reverse transcriptase activity (hTERT) that is responsible for the addition of the telomeric repeats onto the end of chromosome [62,63]. It has been well documented that the expression of telomerase is required for the oncogenic transformation of many normal cell types [64,65]. In the case of the ovary, telomerase is absent in normal ovarian surface epithelium and premalignant lesions, but up-regulated in 95% of ovarian carcinomas [66]. Yang et al. [45] in the in vitro studies found that all LPARs were expressed in various ovarian cancer cell lines. These authors also found that LPA up-regulated hTERT mRNA in ovarian cancer cells through the activation of HIF-1α [45]. Moreover, the mutation of one or two hypoxia-responsive elements (HREs) in the 342 promoter region abolished the induction of hTERT promoter activity by LPA [45]. Taking above facts into consideration, the authors concluded that HIF-1α was required for the transcription activity of LPA on hTERT [45]. The results of the above findings demonstrated that the expression and activity of telomerase in ovarian cancer cells was regulated by LPA, which in turn suggests that telomerase is an important molecule through which LPA exerts its oncogenic effects pointing at LPA as the potential molecular target in the anti-cancer treatment strategies.

In invasion and metastasis of tumor cells matrix metalloproteinases (MMPs) play the same as important role as telomerase. They are proteolytic enzymes which induce extracellular matrix degradation. Especially MMP-2 and MMP-9 have been demonstrated to contribute to the progression of cancer cells [67,68]. Fishman et al. [69] demonstrated that in ovarian cancer cells LPA promoted cell migration and invasion through the activation of MMP-2, while Jeong et al. [70] proved that this active lysophospholipid stimulated cell invasion through the Ras/Rho/ROCK signalling and subsequent MMP-9 production. Moreover, it was found that in ovarian cancer MMP-7 secretion and activation was regulated by LPA [71].

There are many pathways of the action of LPA which show the significant role of LPA in ovarian tumorigenesis. On one hand, in the therapeutic strategies, elevated LPA levels in the serum samples [33] might be exploited as the potential biomarkers of ovarian cancer, even in its early stages. On the other hand, the interactions between LPA signalling and gep proto-oncogene $G\alpha_{12}$ and VEGF expressions or MMP and telomerase activities give the possibility for LPA to become the target molecule for novel chemoprevention agent in clinical cancer approaches.

Lysophosphatidic acid as a therapeutic target in endometrial cancer

Endometrial cancer is a major cause of morbidity and mortality for women worldwide. According to epidemiological data of the Polish National Cancer Registry 2009 it was the fourth most common malignancy among women in Poland, causing 7,3% cases with the incidence ratio of 15/100 000. The mortality ratio was 2.4/100 000, which led to the twelfth place in terms of the causes of cancer deaths in Poland [72]. Most women with endometrial cancer are diagnosed at an early stage with uterine-confined tumors, often after generally known characteristic symptoms like atypical menstrual periods, abnormal vaginal or uterine bleeding [73]. Despite the overall favourable prognosis of endometrial cancer, some women have neoplasms with more aggressive histology, and are at substantial risk of recurrence and death. The main prognostic factors include age, race, stage, grade, depth of invasion, tumor size and cell type [74]. The epidemiology of endometrial cancer is multifactorial. The most important risk factors for endometrial cancer associated with the development of endometrial carcinoma are unopposed estrogen exposure and obesity [75]. Endometrial cancers have been broadly classified into two types [76]. Type I neoplasms, including endometrioid adenocarcinomas, are most common, generally arise from atypical endometrial hyperplasia and are estrogen dependent. Type II cancers include more aggressive histological variants such as clear-cell and serous carcinomas and uterine carcinosarcomas. Non-endometrioid tumors are less common than endometrioid tumors but are associated with disproportionately high mortality. Routinely, endometrial cancer is successfully treated with surgery and/or radiotherapy [77]. However, there is always a gruop of patients with an advanced or recurrent disease, or those who wish to preserve their fertility. Therefore, there is still an increasing demand for introducing more effective, targeted, and less morbid therapies. Moreover the research of the predictive factors of recurrence or death is at least the same as important.

As the potential candidates for targeted anti-cancer therapy, like in the case of ovarian cancer, are also considered the members of LPA family. While the connection between LPA and tumorigenesis in ovaries is fairly well understood, the connection between LPA and endometrial cancer is not well examined. Most of the studies were performed in vitro using the endometrial carcinoma cell line HEC1A. Hope et al. [78] reported that among the four principle LPA receptors (LPAR1, LPAR2, LPAR3, LPAR4), LPAR2 was predominantly expressed by HEC1A cells. It was also documented that the physiological level of LPA stimulated the invasion and proliferation of HEC1A cells [78,79]. Moreover, Wang et al. [79] pointed at LPA as the strong promoter of urokinase plasminogen activator, which elevated levels were correlated with tumor malignancy. What is more, the knockdown of LPAR2 caused the supression of LAP-induced HEC1A invasion, but there was no significant changes in the level of migration of HEC1A cells [79]. Besides, the knockdown of LPAR2 blocked LPA-induced activation of MMP-7 which plays important regulatory role in cell surface proteolysis and is capable of binding to a variety of cell surface proteins, such as E-cadherin, β-integrin and tumor necrosis

factor-α [79]. In endometrial cancer, like in the ovarian cancer, the overexpression of MMP-7 initiates the activation of MMP-2 which promotes cancer invasion [78]. All of the above data suggest the possibility of LPA-dependent targeted molecular therapy also in endometrial cancer.

Conclusion

In this review, we provided updated evidence for LPA signaling via LPARs in ovarian and endometrial cancer cells. Moreover, we had an intention to present LPA as a promising molecular target in the diagnosis and therapy of ovarian and endometrial cancer.

So far, in most reproductive organ associated malignancies, targeted therapies have not entered clinical practice. Despite important advances of clinical trials in the therapy of cancer over the past few decades, treatment failure and mortality rates in the majority of malignant diseases, remain unacceptably high. We suspect that cure rates will not improve significantly unless alternative treatments to conventional chemotherapy regimens are developed. At present, there is no cancer treatment that is based on the inhibition of any of the enzymes responsible for LPA synthesis, LPARs, or signaling downstream of these receptors. Therefore, we suppose that improving our knowledge of the physiological and pathological consequences of LPA signaling may lead to the development of therapeutic agents that will enable us to target this signaling cascade. In particular, we predict that such treatments could be used together with immunotherapy that stimulates host's immune response and with other traditional treatments to achieve better clinical prognosis of ovarian and endometrial cancer patients in the near future.

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