

# Plasma Lysophosphatidic Acid Level: A Diagnostic Tool and Benchmark for Ovarian Cancer Management



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## Abstract

In ovarian cancer there is formation of tumor cells in ovarian tissues. Lysophosphatidic acid (LPA) motivated cell proliferation, migration and endurance by acting on its cognate G-protein-coupled receptors. Lysophosphatidic acid (LPA), present in ascitic fluid, motivates the enlargement of malignant ovarian tumors by raising the appearance of vascular endothelial growth factor (VEGF) in ovarian cancer cells. Ovarian cancer cell progress is repressed by alendronate, a nitrogen containing biophosphate which attenuate the establishment of Rho by blocking the mevalonate pathway.

## Ovarian Cancer

In ovarian cancer there is formation of tumor cells in ovarian tissues. In the US, in about 69 women 1 woman will build up this malignancy during her life span. And, not only this disease occurs in women over the age of 50 but also in women with younger ages [1]. There are many different types of ovarian tumors. Few of them comprise: Ovarian (it is mainly extensive type of ovarian tumor), Ovarian germ cell tumor and Low malignant potential ovarian tumor [2].

## Lysophosphatidic Acid in Ovarian Cancer

Plasma LPA levels may demonstrate that it is a potential biomarker for ovarian cancer and other gynecologic cancers [3]. Significantly high total LPA levels were resolute in the sera of patients with diverse types of tumors benevolent (benign) and wicked (malignant) [4]. Lysophosphatidic acid (LPA), lysophosphatidylinositol (LPI), lysophosphatidylcholine (LPC), and sphingosine-1-phosphate (S1P) appear useful as investigative and predictive biomarkers of ovarian cancer [5]. The women with ovarian cancer and other gynecological cancers had elevated LPA levels than the normal women [6]. LPA in the pathophysiology of human ovarian cancer and possible to other types of human malignancies [7]. LPA flow could be a real addition to the organization

and management of this disease. Additional studies of the LPA flow and other phospholipids in ovarian cancer are important for making obvious their significant roles [8]. Manifestation of LPA2 or LPA3 during ovarian cancer adds to ovarian cancer ferociousness, signifying that the targeting of LPA synthesis and consumption may be noticeable for the cure of ovarian cancer [9]. Considerate the pathway regulating LPA production, metabolism and function could lead to increased ways for in the early hours of finding and to new targets for analysis in ovarian cancer [10]. Lysophosphatidic acid is an intercellular lipid mediator with growth factor-like activities, and is swiftly produced and released from activated platelets to influence and to manipulate the target cells [11]. Different LPA species with different fatty acid chains are the collection of entire LPA. So it was to make a decision whether one or more precise fatty acid LPA species were connected with disease or disease staging. From research experiments, it was concluded that an increased existence of unsaturated fatty acids in plasma LPA/LPI was first established in patients with late-stage or recurrent ovarian cancer and probably with further gynecological cancers because lysophosphatidylinositol (LPI) co-migrates with LPA [12]. The bioactive phospholipid lysophosphatidic acid (LPA) motivated cell proliferation, migration and endurance by acting on its cognate

G-protein-coupled receptors. Aberrant LPA production, receptor appearance and indication almost certainly contribute to cancer establishment, expansion and metastasis. The current recognition of ecto-enzymes that mediate the creation and degradation of LPA, as well as the magnification of receptor-selective analogues, point towards the mechanism by which LPA production or achievement could be adapted for cancer therapy [13]. LPA receptors are necessary for the invasion of ovarian cancerous cells into peritoneal mesothelial cells. Thus human peritoneal mesothelial cells mainly produce biologically active lipid signaling molecules such as LPA. Habituated standard of peritoneal mesothelial cells motivate migration, union and attack of ovarian cancer cells and also perform similar tasks *in vivo* [14]. LPA is a lipid negotiator that fastens to G-protein attached receptors. Epidermal growth factor (EGF) which is known as a polypeptide growth factor, bind to EGF receptor (EGFR) a receptor tyrosine kinase. Two of them show responses in ovarian cancer cells like poliferation, immigration, metastasis and initiation of angiogenesis. LPA has the ability to act as an autocrine / paracrine factor to transactivate Epidermal growth factor receptor (EGFR). So it will show the position of phospholipase-D2 origination in LPA synthesis also it will show connection between EGF and LPA receptor. Over expression of PLD2 increases LPA production. This demonstrates that EGF enhances LPA fabrication in a method that necessitates phospholipase-D2 (PLD2) [15]. LPA is a bioactive phospholipid which motivates continued existence, poliferation, adhesion and passage of ovarian cancer cells all the way through activation of G- protein attached to plasma membrane receptors. LPA and its receptors copiously uttered in high concentration in malignant ascites and in plasma of ovarian cancer patients. LPA indicates numerous intracellular passageways to support growth factors and protease appearance. It also induce cancer cell invasion through extracellular surrounding substance and across basement membrane [16]. LPA proceeds via the cell surface G- protein attached receptors LPA [1-3] to carry out an extensive variety of cellular feedback. It is present at elevated levels in intraperitoneal effusions of human ovarian cancer mounting cell continued existence, poliferation and motility. Appearance of LPA [1-3] receptors was blocked or enhanced in ovarian cancer cells using tiny interfering RNAs (siRNA) and lentivirus build. It is expected that cells with improved appearance of LPA receptors showed more invasiveness. SiRNA reduction blocked both immigration and invasion. It is accomplished that appearance of LPA [2,3] during ovarian cancer improved ovarian cancer ferociousness because LPA receptor shapes primary tumors of size greater than before and increased ascites volume [17]. The recent detection of metabolizing enzymes that intervenes the degradation and development of LPA and expansion of receptor selective analogues opened a potential to come within reach to treat this deadly disorderness. Over expression of these metabolizing enzymes revisit physiologic circumstances and slow down the escalation of cancer cells. They apply their special effects by metabolizing extracellular LPA, so LPA through metabolism, production and

receptors may offer outstanding aim for molecular therapeutics and also helps for early recognition of molecular appearance of LPA. Other lysolipids and enzymes may also smooth the progress of both diagnosis and keep an eye on reaction of a specified patient to heal [18]. LPA is a biologically active phospholipid that is formed from and increases ovarian cancer cells, and encourage immigration, poliferation and endurance. Properties of LPA are demonstrated by G- protein attached receptors of cell exterior that trigger numerous heterotrimeric proteins. G-proteins are neutralized by controller of G- protein signaling (RGS) proteins. This indicates that RGS proteins may adjust G- protein signaling passageway started by LPA in ovarian cancer cells [19]. Studies indicate that LPA motivate both chemotaxis and chemokinesis of ovarian cancer cells. Furthermore, constitutively active H-Ras improves ovarian cancer cell movement while leading negative H-Ras block LPA motivated cell movement signifying that Ras works opposite of G (i) to mediate LPA influence cell movement. Actually LPA activates mitogen-activated protein kinase kinase1 (MEKK1) in a G (i) Ras dependant manner and that MEKK1 activity is vital for LPA motivated cell movement. Inhibitors that inhibit MEKK1 trail are MEK1/2, MKK4/7 and nuclear factor-kappa B pathways do not extensively change LPA motivated cell movement. LPA stimulates the reorganization of main union kinase to focal contact regions of cytoplasm covering and this occurrence is eliminates by pertussis [20]. Ovarian cancer is tremendously metastatic viruses demonstrate by ascites arrangement and transmission i.p. union, incursion, and metastasis. Levels of LPA are eminent in the plasma of patients with ovarian cancer, counting 90% of subjects who have stage 1 disease, which indicates that LPA may maintain early events in ovarian cancer diffusion.

Appearance of matrix metalloproteinases (MMPs) is also up-regulated in ovarian cancer tissues and ascites. An important up-regulation of MMP-dependent proMMP-2 activation was experiential in LPA-treated cells, leading to improved pericellular MMP activity. As a result of enlarged MMP activity, haptotactic and chemotactic motility, *In vitro* wound finished, and attack of an artificial basement membrane were improved. These data designate that LPA contribute to metastatic distribution of ovarian cancer cells via up-regulation of MMP action and succeeding downstream modify in MMP-dependent wandering and determined performance [21]. Lysophosphatidic acid (LPA) relates to a new family of lipid mediators that are endogenous growth factors and that draw out various biological properties, usually with the activation of G protein-coupled receptors. LPA can be produced after cell activation through the hydrolysis of preexisting phospholipids in the membranes of motivated cells. A spectacular rise of LPA levels was established in serum of patients suffering from ovarian carcinoma. Progression of the malignancy is associated with a differential expression of a variety of LPA receptor subtypes. The occurrence of LPA in the follicular fluid of healthy individuals associates that this biological mediator may be related to normal ovarian physiology. LPA persuades proliferation and mitogenic

indicators of prostate cancer cells, and a novel LPA receptor is of form has been documented in healthy prostate tissues. This confirmation designates numerous roles for LPA in both male and female reproductive physiology and pathology [22]. Many reports recommend that lysophosphatidic acid (LPA) up-regulates Fas ligand (FasL) cell surface presentation on the ovarian cancer cells. This was expected to examine soluble FasL (sFasL) secretion linked with the small membrane microvesicles upon LPA stimulation, and to examine the roles of cytoskeletal restructuring in FasL transport induced by LPA [23]. It is established that LPA is a potent inducer of interleukin-6 (IL-6) and interleukin-8 (IL-8) production in ovarian cancer cells. Both IL-6 and IL-8 have been occupied in ovarian cancer development. LPA motivates the transcriptional activity of the IL-8 gene with little consequence on IL-8 mRNA constancy. The most favorable response of the IL-8 gene supporter to LPA relied on binding sites for NF- $\kappa$ B and AP-1, two transcription issues that were strongly activated by LPA in ovarian cancer cell lines. Positive regulators of the NF- $\kappa$ B and AP-1 pathways synergistically activated the IL-8 gene promoter [24,25].

LPA sheltered ovarian cancer cells from anti-Fas-induced apoptosis. Cell lysis and subcellular fractionations confirmed that LPA handling encouraged a translocation of Fas receptors, along with phosphorylated ezrin, from the membrane attached to the actin cytoskeleton, to the cytosol. Translocation of the Fas receptor condensed Fas concentration in the membrane and may slow down its cluster and internalization during early apoptosis induced by anti-Fas. DISC staining demonstrated that LPA reserved Fas receptor aggregation and caspase-8 activation at the membrane, which further inhibited caspase-3 and 7 activation in the cytosol [26]. Lysophosphatidic acid (LPA), at concentration present in ascitic fluid, ultimately motivates the enlargement of malignant ovarian tumors by raising the appearance of vascular endothelial growth factor (VEGF) in ovarian cancer cells. It is concluded that in spite of formerly defined indirect mechanism that enhances angiogenesis via VEGF, LPA may straightforwardly enhances the rank of cyclin D1 in ovarian cancerous cells, enhancing their propagation [27]. Tissue hypoxia has been observed as a serious factor for tumor aggressiveness and metastasis is one of the quickly growing tumors. Ovarian cancer is a quick growing tumor, and highly developed ovarian cancer patients have large amount of ascites.

Ovarian cancer ascites hold different growth factors counting bioactive lipids. LPA is recognized as an ovarian cancer activate factor in ascites of ovarian cancer patients. In addition of tissue hypoxia, massive ascites of ovarian cancer is also a hypoxic situation, which may be related to LPA production. The effects of hypoxia on cellular responsiveness to LPA were observed in different cells derived from ovary; immortalize human ovarian surface epithelial cell (HOSE), primary borderline tumor and malignant tumor cells, and ovarian cancer cell line (SKOV3). After illuminating these cells to hypoxia it is originates that cell migration was improved by hypoxia in all of cell types tested. In contrast, invasion was enhanced in the primary

ovarian cancer cells but not, the benign and borderline cells. SO LPA production is improved by hypoxia and cancer cells are sensitized to LPA by hypoxia [28]. Fasudil (1-[5-isoquinolinesulfonyl]-homopiperazine; HA-1077) is a drug that has been in clinical use in Japan for the avoidance of vasospasm after subarachnoid hemorrhage and is known to be a powerful ROCK-specific inhibitor. Fasudil extensively reserved LPA-induced attack and motility of human ovarian cancer cells in a dose-dependent manner. Moreover, fasudil originates the loss of intracellular cytoskeletal reorganization, which is essential for cell motility, such as anxiety fiber formation and focal adhesion assembly. Fasudil suppressed LPA-induced tyrosine phosphorylation of paxillin, a representative focal adhesion protein, and serine phosphorylation of myosin light chain, which are required for the system for cell passage fasudil attenuated the invasiveness of human ovarian cancer cells with the self-consciousness of the LPA/Rho/ROCK pathway [29]. Both vascular endothelial growth factor (VEGF) and lysophosphatidic acid (LPA) are buried under the ovarian cancer cells and are recognized to hold cancer cell enlargement through the precise mechanism(s) are not exclusively understood. Since telomerase, a ribonucleoprotein uttered in 95% of ovarian cancers, plays an important role in cellular immortalization, expansion, and tumor development [30].

The levels of total LPA and its species in women with ovarian cancers were considerably higher from those in healthy women ( $p < 0.001$ ). No considerable difference was found in the levels of total LPA or any of its species between the women with benign and those with malignant ovarian cancers [31]. LPA levels are constantly high in the plasma and ascites of ovarian cancer patients, but not in most other epithelial tumors, with the exclusion of cervix and endometrium, signifying that LPA may be of particular importance in the pathophysiology of ovarian cancer. Increased levels of LPA, distorted receptor expression and changed responses to LPA may account to the beginning, succession or conclusion of ovarian cancer [32]. Transcriptional actions mediated by LPA in the cancer microenvironment control cancer succession through intonation of cell adhesion molecules like claudin-1 and account an LPA-mediated expression mark in ovarian cancer that demonstrates a poorer diagnosis [33]. The plasma concentrations of individual LPA species and total LPA are not different in ovarian cancer patients and control subjects. Patients with ovarian cancer have fairly elevated total plasma LPA levels than did control subjects. LPA levels in malignant effusions, including ovarian cancer, were considerably increased compared with those in control subjects. In addition, the grade array of individual LPA species differs between LPA in plasma and malignant effusions between patients with ovarian cancer [34]. Strong growth-promoting activity toward human ovarian cancer cells is contained in ascites of ovarian cancer patients which is related with quick increase in cytosolic free calcium [Ca<sup>2+</sup>].

The ability of OCAF (ovarian cancer activating factor) to increase cellular calcium due to phosphoinositide hydrolysis may exist in

the structure and/or place of the fatty acyl sequence of LPA due to phosphoinositide hydrolysis. Purified OCAF having concentrations similar to the concentrations present in ascites from ovarian cancer patients is enough to stimulate production of ovarian cancer cells. Even at best concentrations of OCAF, production was lower than ascites from ovarian cancer patients, representing that, even though OCAF may be a chief controller of ovarian cancer cells *in vivo*, it is not the single mediator present in ascites [35]. Autotoxin (ATX) is a cancer cell motility-modifying factor which is initially secluded from malignant cells supernatants. ATX demonstrate its effects via 5'-nucleotide pyrophosphatase and phosphodiesterase actions. The fabrication of the biologically active phospholipid mediator, lysophosphatidic acid from lysophosphatidylcholine (LPC), is catalyzed by Lysophospholipase D (lysoPLD) which is identical to ATX. Chemotaxis and propagation of several diverse cell lines is noticeably improved by recombinant ATX mainly in the company of LPC. Considerable amount of LPC is released by several cancer cell lines, a substrate for ATX, into the culture medium. It is concluded that autocrine or paracrine synthesis of LPA adds to cancer cell motility, endurance, and propagation by determining that ATX and lysoPLD are alike [36]. In many of the pathophysiological states including ascitic fluid from ovarian cancer patients lysophospholipid levels are high *in vivo* which indicates a role in the pathophysiology of this overwhelming disease. Though in the blood of cancer patients contentious levels of particular lysophospholipids may be changed which provides a potential method for early diagnosis. Several enzymes responsible for metabolism of lysophospholipids are abnormal in ovarian and other cancers. Lysophospholipid receptor expression is also abnormal in cancer cells from multiple dissimilar lineages. Lysophospholipid cell surface receptors belong to the family of G protein attached receptor. 40% of all drugs in current use target lysophospholipid receptors which shows they are highly "druggable" [37]. Particular cell-surface G protein-coupled receptors (GPCRs) that initiate cell growth, propagation, and endurance pathways and also show distorted appearance of cancer cells are activated by lysophospholipids. In the cancer microenvironment possible sources of lysophospholipids consist of cancer cells and stroma, for instance mesothelial cells, inflammatory cells and platelets which are activated by proinflammatory cancer environment. The dispersion of lysophospholipids from the cancer microenvironment into the bloodstream shows, they have the ability to provide an early analytical marker and possible monitoring of cancer response to treatment [38].

Autotoxin (ATX) or nucleotide pyrophosphatase/phosphodiesterase 2 (NPP2) is a member of NPP family which increases cancer cell motility, experimental metastasis, and angiogenesis. ATX produces the lipid mediator lysophosphatidic acid (LPA) from lysophosphatidylcholine by mainly acting as a lysophospholipase D. LPA and sphingosine 1-phosphate (S1P) potently and particularly repress ATX in a mixed-type manner. The homologous ecto-phosphodiesterase NPP1 is insensate to LPA and S1P, because it lacks

lysophospholipase D action. LPA can control its own production in the extracellular surroundings, by repressing ATX action which divulges an original role for S1P as an inhibitor of ATX, in spite of its role as a receptor ligand [39].

### Management of Ovarian Carcinoma and Lysophosphatidic Acid

For cell type-specific treatment reproducible analysis of ovarian cancer cell types is hazardous for cell type-specific treatment. To test the reproducibility of cell type analysis in Canada after concise guidance in the use of customized World Health Organization criteria reproducibility of histologic tumor type was done amongst 6 pathologists to categorize ovarian cancers into 1 of 6 types. These are high-grade serous, endometrioid, clear cell, mucinous, low-grade serous, and other [40]. Inhibin, and calretinin, epithelial membrane antigen (EMA) may greatly aid by synchronization the difference among a sex cord cancer and an endometrioid cancer with sex-cord-like pattern the final two being naturally positive and EMA negative in sex cord cancers, the contrary being distinctive of endometrioid carcinoma [41]. To the rising list of WT1-positive cancers ovarian Sertoli cell cancer should be supplementary. For the difference of Sertoli cell cancer from endometrioid cancers and carcinoid this marker is useful the investigative usefulness of WT1 in Sertoli cell cancer is analogous to inhibin but superior to that of calretinin [42].

Ovarian cancer cell progress is repressed by alendronate a nitrogen-containing bisphosphonate which attenuates the establishment of Rho by blocking the mevalonate pathway. Histologic inspection discovered that alendronate treatment reduces the stromal attack of the i.p. cancer while blocking the metalloproteinase-2 movement in ascites. The powerful effects of alendronate in decreasing stromal attack, cancer load, and ascites propose that it will be helpful for dealing of women with ovarian cancer. In addition, alendronate administration reduced the serum CA-125 levels [43]. Endurance of women with complex ovarian cancer by 16 months is boosted by giving high doses of chemotherapeutic drugs which is called by experts a big advance against the most lethal cancer in women. This treatment is so tough and normally 6 in 10 women does not bear it and toggle to intravenous chemotherapeutic drugs [44]. Tissue type transglutaminase (TG2) is an inimitable multifunctional protein that performing a role in many ladders in the tumor metastatic flow. Patient endurance in both univariate and multivariate analyses is considerably poorer due to over expression of TG2. It is suggested that TG2 overexpression in ovarian cancer is an unfavorable predictive aspect and targeting of TG2 may be an outstanding beneficial advance [45]. A human ovarian adenocarcinoma cell line (PE04) which is estrogen receptor positive is accepted as a xenograft and its development is increased by 17  $\beta$ -estradiol at concentrations from 10<sup>-6</sup> and 10<sup>-12</sup> M. Ovarian cancer cells which are ER +ve are responsive to 17  $\beta$ -estradiol *in vivo* but the reaction is different *In vitro*. Ovarian cancer is hormone susceptible and often responsive to endocrine treatment [46]. In ovarian and

other cancers overexpression of Focal adhesion kinase (FAK) is commonly seen and shows reduced medical conclusion. *In vitro*, phosphorylation of FAK is repressed by TAE226 which is inhibitor of FAK. It also repress the cell growth in a time and concentration dependent relative method. *In vivo*, cancer load is considerably lowered by FAK blockage by TAE226. The curative efficiency of TAE226 is associated with introduction of apoptosis of cancer linked endothelial cells, and lowered microvessel thickness and cancer cell propagation [47]. Inflammation may motivate ovulatory actions as a seditious response is produced during the process of ovulation. Extra threat factors for ovarian cancer, include asbestos and talc contact, endometriosis (i.e., ectopic implantation of uterine lining tissue), and pelvic inflammatory disease, may not straightly connected to ovulation or to hormones rather they cause pelvic inflammation. The opportunity that inflammation is a pathophysiologic provider to the progress of ovarian cancer concludes an approach to future research [48]. Over about 20 years due to extra efficient surgical procedures and handling with combinations of cytotoxic drugs, the 5-year endurance for ovarian cancer patients has significantly enhanced, but the overall treatment rate leftover around 30%. By translating current insights at the molecular and cellular levels enhancement in long-term endurance may be done to improve personal techniques for handling [49]. Ovarian tumor ascites when compared with ascites of non-malignant diseases it is noted that they have naturally occurring alkyl- and alkenyl-lysophosphatidic acids (al-LPAs) at increased levels. They motivate DNA production and propagation of ovarian tumor cells. They also motivate cell movement and the discharge of interleukin-8 (IL-8) in ovarian cancer cells. These pathways are actually linked to cancer metastasis and angiogenesis [50]. The frequent epithelial ovarian tumors which indicate around 90% of all ovarian tumors, occur from the 2-cell epithelial casing of the outer layer of the ovary [51].

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