

Angiogenic effect of lysophosphatidic acid receptors on cervical cancer cells

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Abstract: Cervical cancer was recently reported to be the fourth leading cause of cancer death in women worldwide, causing an estimated 265,700 deaths a year. This malignancy is typically treated by radical surgery during the disease's early stages, by radiotherapy combined with chemotherapy for locally advanced cases, and by chemotherapy for metastatic or recurrent cases. For advanced cases, development of targeted therapies to supplement traditional treatments may contribute to the interference of tumor growth and invasion and to the improvement of patient survival. Since angiogenesis plays an important role in the progression of cervical cancer, angiogenic factors are potential targets. Vascular endothelial growth factor (VEGF) and interleukin-8 (IL-8) are the two most potent angiogenic factors. Adding bevacizumab, a recombinant humanized monoclonal antibody and VEGF antagonist, to chemotherapy regimens for recurrent cervical cancer has been shown to prolong median overall survival (OS) by 3.7 months. Lysophosphatidic acid (LPA), a naturally occurring lipid and autotoxin (ATX), is a major LPA-producing enzyme. In cervical cancer cells, LPA may activate LPA receptors LPA2 and LPA3 and play an important role in tumor growth through IL-8-dependent angiogenesis. The usefulness of a molecular therapy which targets the ATX-LPA-IL-8 cascade for the treatment of advanced cervical cancer merits further investigation.

Keywords: Lysophosphatidic acid (LPA); angiogenesis; interleukin-8 (IL-8); cervical cancer

Submitted Aug 29, 2015. Accepted for publication Oct 01, 2015.

doi: 10.3978/j.issn.2218-676X.2015.10.09

View this article at: <http://dx.doi.org/10.3978/j.issn.2218-676X.2015.10.09>

Introduction

Cervical cancer is a common solid tumor malignancy (1-7), with racial/ethnic, socioeconomic, and geographical disparities in incidence and mortality (8-20). A 2015 study reported that in 2012 there were an estimated 527,600 new cases and 265,700 deaths worldwide from cervical cancer, which has the fourth highest incidence rate and is the fourth leading cause of cancer death in women (21). In a study using data from the Surveillance, Epidemiology, and End Results Program, after adjusting for confounding factors such as race, marital status, stage, age, treatment, grade,

and histology, for cervical cancer there was a significant difference in specific mortality from 1985 to 1989 and from 1990 to 1994 (but not after 1995) (18). Cervical cancer's high incidence rate and its persistently high mortality highlight its importance as a woman's health issue.

The standard treatment for cervical cancer's early stages is radical hysterectomy, with more conservative therapies being used for younger patients (22-26). For locally advanced stages, concomitant chemotherapy and radiotherapy are used (27-32). Recurrent and metastatic disease are treated usually by palliative platinum-based chemotherapy, which possesses a limited utility and can

cause significant adverse side-effects (33-38). For advanced cases, research dedicated to molecular targeted therapies has become a promising means of seeking out novel agents that improve patient prognosis and reduce side effects (39-41).

Clinical evidence of angiogenesis in cervical cancer

Formation of new blood vessels is crucial for tumor growth, progression and metastasis. Within the growing tumor, angiogenesis is required for formation of new blood vessels and for recruiting and sustaining its blood supply (42,43). The progression from cervical cancer precursor (CIN) lesion to invasive carcinoma can be a process of converting dormant tumors. Clinical observations have shown that angiogenesis occurs in both pre-invasive and invasive cervical cancers and are linked to clinical symptoms such as spontaneous bleeding and easy bleeding upon contact (44-47).

Angiogenesis is connected with diagnosis. Preinvasive and invasive cervical cancers present distinct features—i.e., microvessel growth along with persistent cell production—which clinically can be directly visualized by colposcopy after magnification (48,49). In correspondence with these colposcopic findings, histological examination of tumor sections has revealed that malignant cervical cancer cells are surrounded by highly tortuous vessels with no uniform direction or branching and by irregularly formed vascular spaces (50). Moreover, during the progression from noninvasive to microinvasive cervical carcinoma, microvessel density (MVD)—a measure of tumor angiogenesis—has been reported as increasing significantly (51). In fact, the different vascular patterns which present themselves between pre-invasive and invasive cancer can be used for pre-treatment differential diagnosis (52). Such angiogenic patterns make cervical cancer one of the most effectively diagnosed of all cancers.

Using 3-dimensional power Doppler angiography, tumor vascularity assessed for cases of cervical cancer all showed intratumoral blood flow (53). Ultrasound also showed a chaotic network of tortuous vessels traversing the cervical cancer tumor mass (54). A significant positive correlation between tumor vascularization and cervical volume has also been found (55).

Angiogenesis is also linked with prognosis. It may affect survival in both early- and advanced-stage cervical cancer patients. Up-regulation of angiogenic factors correlated with severity of CIN lesions and invasive disease (56). In cervical cancer, the angiogenic factors angiogenin,

endoglin and endostatin show a definite relationship with disease stage (57). Among 215 healthy subjects and 199 early cervical cancer patients who had been treated with surgical resection, Kim *et al.* found that polymorphisms of vascular endothelial growth factor (VEGF) genes may affect cancer susceptibility and survival in cases of early cervical cancer by modulating tumor angiogenesis (58). MVD is an independent prognostic parameter for recurrence-free survival in patients with early stage cervical cancer who undergo radical hysterectomy with pelvic lymph node dissection; MVD at or above the cut-off point of nine vessels per high power field had significantly poorer recurrence-free survival (59). In eighty-seven patients with cervical cancer who underwent definitive radiotherapy with a combination of external beam radiotherapy (45-50.4 Gy) and high-dose-rate brachytherapy (5×7 Gy), Dunst *et al.* found that poorly oxygenated tumors had a significantly increased MVD, a fact which had an overwhelming impact on local failure rate and survival (60). Higher tumor vascularity was associated with lower overall survival (OS) and locoregional control in carcinoma of the cervix treated with radiotherapy (61). Randal *et al.* used semi-quantitative immunohistochemical staining to examine cervical cancer tissue for VEGF, thrombospondin-1 (TSP-1), CD31 and CD105. They found that high levels of CD31 MVD, but not TSP-1, VEGF or CD105 MVD, was an independent prognostic factor for progression free survival. Tumor angiogenesis measured by CD31 MVD was an independent prognostic factor for cervical cancer (62). In 166 patients with stage IB cervical cancer treated primarily by radical hysterectomy and bilateral lymphadenectomy, high MVD was found to be an independent prognostic factor which adversely influenced patients' survival (63).

Histological evidence of angiogenesis in cervical cancer

Angiogenesis in cervical cancer can be directly evaluated by microvessel immunohistological staining and counted under a microscope (64). *Table 1* shows studies that investigated both angiogenesis and MVD in cervical cancer.

In cervical cancer, histological sections immunostained for CD31 were quantitatively evaluated for MVD (51,58,62,65-68). Besides CD31, CD34 was the other frequently used angiogenesis marker (69-71). In a nude mice model study, it was shown that a combination of interleukin (IL)-24 and cisplatin inhibited tumor growth and angiogenesis and that these effects were mediated by

Table 1 Selected clinical references investigating angiogenesis and microvessel density (MVD) in cervical cancer

Authors	Methods	Results	Comments	Reference
Tajima <i>et al.</i> (1999)	Staining with the specific endothelial marker anti-CD31 was used to study MVD in 75 patients with grade 3 cervical intraepithelial neoplasia and in 20 patients with microinvasive cervical cancer	MVD was significantly higher in invasive cancer than in grade 3 cervical intraepithelial neoplasia	During the progression from noninvasive to microinvasive cervical carcinoma, MVD increases significantly. However, vessel density does not predict recurrence of noninvasive lesions	(51)
Kim <i>et al.</i> (2010)	Angiogenesis measured by CD31 MVD	Angiogenesis measured by CD31 MVD was found to be significantly lower in patients with the VEGF + 405C/C genotype and the VEGF -2578C - -460T - +405C haplotype	VEGF gene polymorphism plays a role in early cervical cancer susceptibility, angiogenesis, and survival	(58)
Randall <i>et al.</i> (2009)	Semi-quantitative immunohistochemical (IHC) staining was used to test 173 tumor specimens for the presence of vascular endothelial growth factor (VEGF, pro-angiogenesis factor), thrombospondin-1 (TSP-1, anti-angiogenesis factor), CD31 (non-specific endothelial marker), and CD105 (tumor-specific endothelial marker)	High CD31 MVD, not VEGF, was an independent prognostic factor for progression-free survival (PFS) and overall survival (OS)	Tumor angiogenesis measured by CD31 MVD is an independent prognostic factor for both PFS and OS in high-risk, early-stage cervical cancer	(62)
Sharma <i>et al.</i> (2013)	180 patients with suspected colposcopic findings were subjected to a colposcopic-directed biopsy. Biopsy tissue was sent for histopathological examination; out of these, 50 biopsied samples were sent for immunostaining of CD-31	CD31 showed MVD was higher in both preinvasive and invasive groups	Angiogenesis is a marker of tumor progression	(65)
Dellas <i>et al.</i> (1997)	Histological sections immunostained for CD31 were quantitatively evaluated for MVD	Comparison of microvessel counts from normal epithelium with those from CIN and invasive carcinoma showed significant increases in precancerous lesions and invasive cancer	This study shows that MVD is a strong independent prognostic indicator for overall survival in patients with clinical stage IB cervical carcinoma	(66)
Biedka <i>et al.</i> (2012)	A quantitative sandwich enzyme immunoassay (ELISA) was used to determine serum VEGF. All tumor samples were examined immunohistochemically using podoplanin and anti-CD31 antibodies	A statistically significant correlation was discovered between MVD and lymphatic vessel density (LMVD) in cervical cancer	MVD and LMVD play an important role in tumor growth and progression in cervical cancer	(67)

Table 1 (continued)

Table 1 (continued)

Authors	Methods	Results	Comments	Reference
Huang <i>et al.</i> (2014)	CD31 staining was used to count tumor MVD	Coinjection of cancer-associated human cervix fibroblasts enhanced tumorigenesis of cervical cancer cells; an increase of MVD and dye retention was seen in tumor vasculature	This study suggests cancer/stroma cross-talk induced the repression of miR-126 and the upregulation of the proangiogenic gene adrenomedullin (and probably other proangiogenic factors) so as to facilitate angiogenesis and invasion	(68)
Song <i>et al.</i> (2011)	VEGF expression and microvascular density of cervical cancer tissue were detected using immunohistochemistry and CD34 labeling, respectively	Tumors with EFEMP1 overexpression showed a faster growth rate and had a higher level of VEGF expression and microvascular density	EFEMP1 promoted angiogenesis and accelerated the growth of cervical carcinoma <i>in vivo</i> through a VEGF up-regulation pathway	(69)
Wang <i>et al.</i> (2015)	MVD was evaluated by IHC analysis of CD34 expression	Combination of IL-24 and cisplatin inhibits tumor growth and angiogenesis	These effects are mediated by VEGF and PDGF expression	(70)
Vieira <i>et al.</i> (2005)	Tissue samples from 62 patients with invasive cervical carcinoma were stained with a primary monoclonal antibody specific for CD34	MVD was higher in undifferentiated carcinomas	This study suggests that anti-CD34 antibody reactivity in cervical carcinoma is associated with patho-anatomical features indicative of a poorer prognosis	(71)
Chen <i>et al.</i> (2012)	MVD in xenograft tumors in SCID mice was assessed and then quantified using an immunohistological reaction to CD31	Activation of LPA receptors 2/3 mediated IL-8 expression, angiogenesis, and tumor growth	This study suggests that IL-8 is the dominant angiogenic factor in cervical carcinogenesis	(72)

downregulation of both VEGF and platelet-derived growth factor (PDGF) expression (70).

For MVD, a statistically significant difference has been found between poorly differentiated and well-differentiated carcinomas (73). A comparison of microvessel counts from normal epithelium with those from CIN and invasive carcinoma showed a significant increase in MVD expression in precancerous lesions and invasive cancer.

Angiogenesis is an early event in premalignant changes of the cervix. A comparison of MVD levels between low- and high-grade pre-invasive cervical lesions revealed a statistically significant increase in the more advanced lesions (73,74). Large vascular structures were noted in the upper layers of the epithelium with neovascularization of stromal vascular papillae protruding toward the epithelial surface; clinically this is connected with the colposcopic finding of an abnormal vascular image of dysplastic lesions. The amount of angiogenesis appeared to be independent of the human papillomavirus (HPV) type (75).

Lysophosphatidic acid (LPA) concentrations

LPA is a naturally occurring, potent lysolipid present in human blood. LPA's sources include plasma lipoproteins (76), cancer cells (77-79), fibroblasts (80), adipocytes (81-83), peritoneal mesothelial cells (84), and activated platelets (85,86). The measurement of total LPA levels can be performed by radioenzymatic, fluorometric, colorimetric, or immunoenzymatic assay. However, determination of LPA molecular species requires the use of techniques that include capillary electrophoresis, gas chromatography, thin layer chromatography, liquid chromatography, matrix-assisted laser desorption/ionization, and electrospray ionization mass spectrometry (ESI-MS) (87-98). The best method is ESI-MS, which can measure LPA species without interference from other compounds (88-90,93,94,96,98).

Meleh *et al.* used ESI-MS to determine LPA levels and reported that LPA's mean level in the sera of 50 healthy controls was 2.9 μM (99). In a study of 10 controls (8 healthy women and 2 women with benign gynecologic disease), Xiao *et al.* used ESI-MS to show that the plasma LPA levels were below 2.0 μM (96). Using an enzymatic cycling assay, Hosogaya *et al.* reported that in healthy subjects LPA's mean physiological level in women was higher than that in men (76). Using gas chromatography analysis, Xu *et al.* found that for 48 healthy controls the mean LPA plasma level was 0.6 μM (range, <0.1-6.3 μM) (95).

LPA concentrations were found to be significantly elevated in the sera from ovarian, cervical, and some endometrial and peritoneal cancer patients and in the ascites from ovarian cancer patients (94-104). It has been suggested that LPA is a potential marker for the screening, diagnosing, and monitoring of ovarian cancer (95,99,100). Xu *et al.*, using gas chromatography analysis, found that 48 ovarian cancer patients had significantly higher plasma LPA levels (mean 8.6 μM) when compared with 48 healthy controls (95). Using ESI-MS, Xiao *et al.* later confirmed that LPA was elevated in blood specimens from 8 patients with ovarian cancer and one with endometrial cancer (96). Gas chromatography analysis was used to discover that different LPA species were associated with late-stage or recurrent ovarian cancer (97). A meta-analysis done by Li *et al.* of a total of 980 ovarian cancer patients, 872 benign controls and 668 healthy controls revealed that LPA plasma levels in ovarian cancer patients were significantly higher than in benign controls and healthy controls (101). Using ESI-MS analysis, Meleh *et al.* reported that the mean LPA level for 50 ovarian cancer patients and for 65 women with benign ovarian tumor was 8.4 and 8.0 μM , respectively, and that the cut off value for the presence of ovarian tumors was 3.9 μM (99).

When electrogenerated chemiluminescence was used to analyze LPA concentrations in plasma, LPA levels from 135 cervical cancer patients (5.11 \pm 1.92 μM) were found to be significantly higher than those from 40 healthy controls (2.31 \pm 0.45 μM) (103). After using gas chromatography analysis, Xu *et al.*, reported that in 6 cervical cancer patients the mean level for total plasma LPA was 21.9 μM (95). However, ESI-MS is rarely reported as being used to discern LPA species in cervical cancer, and thus further studies are needed.

In instances where liquid chromatography/mass spectroscopy were used to study peritoneal effusion, LPA concentrations were found to be higher in the peritoneal effusions from 10 ovarian cancer patients than in those from 22 nonmalignant patients (102). In peritoneal fluid analyzed using a neurite retraction bioassay, LPA-equivalent levels were 50.2 μM (range, 5.4-200 μM) for all 62 patients and 94.5 μM (range, 15-200 μM) for 13 ovarian cancer patients (104). Using ESI-MS, Xiao *et al.* also found that LPA in the ascitic fluid from 15 patients with ovarian cancer (mean 18.9 μM) was higher than that found in the fluid from 15 patients with benign liver disease (mean 2.9 μM) (98).

Overall, LPA concentrations were found to be higher in

blood specimens from cervical or ovarian cancer patients than in those from healthy controls, and higher in ascitic fluid from malignancies than from non-malignancies.

Autotaxin (ATX) as a LPA-producing enzyme

LPA is present in both cells and biological fluids. In serum or plasma, LPA is produced predominantly by a plasma enzyme called ATX (105-107). ATX (nucleotide pyrophosphatase-phosphodiesterase 2), a secreted lysophospholipase D (lysoPLD) present in serum, is an enzyme that catalyzes the hydrolysis of lysophosphatidylcholine (LPC) into LPA (108). There are two LPA production pathways which convert phospholipids to LPA: (I) the PLA1/PLA2-lysoPLD pathway, where lysophospholipids (LPLs) that are generated by a phospholipase A1 (PLA1) or PLA2 reaction are subsequently converted to LPA by a lysoPLD reaction; and (II) the PLD-PLA1/PLA2 pathway, where phosphatidic acid generated by a phospholipase D or diacylglycerol kinase reaction is subsequently converted to LPA by a PLA1 or PLA2 reaction (106). In blood plasma, LPC is the most abundant phospholipid; ATX is considered the major LPA-producing enzyme in human blood, one which produces the most extracellular LPA (109-111).

In healthy subjects, Hosogaya *et al.* found that plasma LPA concentrations strongly correlated with lysoPLD activity. Lipid-related parameters other than LPC correlated only slightly or did not correlate with the LPA concentration, which suggests that conversion to LPC by lysoPLD might be the major route for LPA production in plasma (76). Although there are other LPA-producing pathways independent of ATX, a strong association between cancer cells and ATX production has been observed. Accumulating evidence for the physiological and pathological functions of ATX strongly support the claim that ATX is an important and promising therapeutic target (112,113).

During mice development, van Meeteren *et al.* noted that ATX was essential for blood vessel formation (114). In 50 cultured human tumor cell lines derived from various tumors (CNS, lung, breast, stomach, colon, kidney, ovary, prostate, cervix, fibroblast, and melanoma), Kishi *et al.* found that some cells expressed a significant amount of ATX at both the mRNA and protein levels. Both ATX protein and lysoPLD activity were detected in the culture supernatants. The highest ATX expression was in SNB-78 cells. Most ATX protein was detected in culture cell supernatant, whereas only a small amount was detected in

cells. These results confirm that ATX is secreted by cancer cells (115).

ATX may promote cell migration, metastasis, and angiogenesis, and has been intimately linked with cancer development. According to Umezue-Goto *et al.*, a variety of cancer cell lines (A-2058, CHO-K1, MDA-MB-231, parental RH7777 and RH7777-EDG2 cells) release significant amounts of LPC, a substrate for ATX, into the culture medium (108). Research on the use of ATX inhibitors, both as a primary and as an adjuvant therapy, is accelerating (110). After oral administration to mice of 3 mg/kg of FTY720, a competitive inhibitor of ATX, significantly reduced plasma LPA levels were noted (116). Murph *et al.* found that in melanoma, vinyl sulfone analogs of LPC irreversibly inhibited ATX and prevented angiogenesis in melanoma (117). Benesch *et al.* discovered that inhibition of ATX with a new ATX inhibitor, ONO-8430506, delayed breast tumor growth and lung metastasis in BALB/c mice (111).

As was the case for LPA, high expression of ATX in cancers is also associated with increased tumor progression, angiogenesis and metastasis (109). The ATX-LPA signaling axis has emerged as an important factor in many types of cancer. These results thus suggest that ATX-targeting strategies may provide a novel therapeutic approach to the inhibition of cervical cancer angiogenesis.

Functions mediated by LPA

LPA mediates a variety of cellular responses. Its physiologic and pathologic functions include the promotion of cell proliferation (118-131), cell survival (124,132-139), cell apoptosis (140-150), cell motility (91,115,151-158), cell migration (119,122,128,150,158-178), cell shape (179,180), cell differentiation (83,125,134,140,169,181-187), gene expression (188-202), cell transformation (203,204), tumorigenesis (139,205-209), cell invasion and metastasis (124,166,170,210-220) and other cell processes. LPA also enhances angiogenesis (72,118,221-229).

LPA receptors in cancer cells

The cellular responses elicited by LPA are produced by signaling through at least six G-protein coupled receptors (GPCRs) (230-243). LPA receptors were originally defined as an endothelial differentiation gene (Edg) family of GPCRs. However, at present LPA's GPCRs are thought of as being divisible into two families: the Edg family

(106,205,233,241,244-262) and the P2Y family (78,106,205, 236,238,240,243,262, 263).

The Edg-family LPA receptors consist of LPA1/Edg2 (247,251,252,255,256,259-262,264), LPA2/Edg4 (230,258,262,265), and LPA3/Edg7 (231,253,262). The p2y-family LPA receptors are the newly discovered GPCRs for LPA, which include LPA4/GPR23/p2y9 (240,262), LPA5/GPR92/93 (235,262), LPA6/p2y5 (236,242,262), GPR87/95 (243,262) and p2y10 (238,262). Among the p2y-family, LPA4, LPA5 and LPA 6 are purinergic receptors. The six protein receptors that interact with LPA were named LPA1-LPA6, with italicized gene names *LPA1-LPA6* representing human genes and *Lpar1-Lpar6* representing non-human genes (266).

LPA receptor expression (LPA1, LPA2, LPA3, and LPA4) has been examined in 50 tumor cell lines from various origins by using quantitative RT-PCR; results revealed that LPA1 was dominant in brain tumor cells, LPA2 was predominantly expressed in cells from colon, stomach, and breast cancers, and LPA3 was expressed in certain ovarian and prostate cancer cell lines. Overall, expression of LPA4 was fairly low (115).

Each LPA receptor in cancer cells has also been studied in the context of their respective cell lines. Up-regulation of LPA1 that promoted pathological functions in cancer cells was found in human pancreatic cancer cell lines (BxPC-3, CFPAC-1, PANC-1, PK-1, YAPC-PD and YAPC cells) (154,156,267), a breast cancer cell line (MDA-MB-231 cells) (268,269), gastric cancer cell lines (AGS, MKN1, MKN28 and MKN74 cells) (269-271), a colon cancer cell line (DLD1 cells) (270), ovarian cancer cell lines (A2780CP, Caov-3, Dov-13, HEY, OVCA432, OVCAR-3 and SKOV-3) (272-275), a melanoma cell line (B16F10 cells) (220), and prostate cancer cell lines (LNCaP, LNCaP-LPA1 and PC3 cells) (130,276-278).

LPA2 expression was found in colon cancer cell lines (CaCo-2, DLD1, HCT116, LS174T, LoVo, SW48 and SW480 cells) (196,270,279-283), ovarian cancer cell lines (3AO, A2780, A2780CP, CaOV-3, DOV-13, HEY, HOC-1, OCC-1, OVCA 420, OVCA 429, OVCA 432, OVCA 433, OVCAR-3 and SKOV3 cells) (152,272-274,284-286), pancreatic cancer cell lines (BxPC-3, CFPAC-1, HPD-K2, PANC-1, PK-1 and YAPC-PD cells) (154,172,267), a gastric cancer cell line (AGS cells) (270), a prostate cancer cell line (PC-3 cells) (277), and thyroid cancer cells (287).

LPA3 expression was found in colon cancer cell lines (DLD1, HCT116, LS174T and SW480 cells) (270,282,283), pancreatic cancer cell lines (BxPC-3,

CFPAC-1, PANC-1, PK-1 and YAPC-PD cells) (154,267), ovarian cancer cell lines (3AO, A2780CP, Caov-3, OVCAR-3, Dov-13, HEY, OVCA432 and SKOV-3 cells) (272-275,285), a gastric cancer cell line (AGS cells) (270), and a prostate cancer cell line (PC-3 cells) (277,278,288).

LPA4, LPA5 and LPA6 play diverse roles in the activation of tumor progression in pancreatic cancer cell lines (PANC-sh4, PANC-sh5 and PANC-sh6 cells) (289). LPA4 was expressed in both human colon cancer cell lines (CaCo-2, DLD1, HCT116, LoVo, SW48, and SW480 cells) (196,285) and a human ovarian cancer cell line (SKOV-3) (290). LPA5 was expressed in human colon cancer cell lines (CaCo-2, DLD1, HCT116, LoVo, SW48 and SW480 cells) (196). LPA5 was also expressed in a human melanoma cell line (B16F10 cells) (220). Like other known P2Y receptors, GPR87 was found to be located mainly on the cell surface, with the overexpression of GPR87 found preferentially in squamous carcinoma cells (291). The presence of other non-Edg and non-purinergic family LPA receptors in cancer cell lines has rarely been reported.

In contrast with studies of other cell lines, studies of LPA receptors in cell lines from cervical cancers are relatively scarce. A report from Chen *et al.* found that the LPA receptors expressed in cervical cancer cells are the Edg-family receptors LPA1, LPA2 and LPA3, which were noted as being up-regulated in cervical cancer cell lines (CaSki, HeLa and SiHa cells) (72). Glatt *et al.* found that up-regulation of both GPR87 transcript and protein was detectable in cervical cancer samples, most often in squamous cancer. They demonstrated that GPR87 contributes to the proliferation and survival of tumor cells (291).

Angiogenic factors in cancer

Angiogenesis is a complex process that plays an essential role in tumor growth and metastasis (292,293). In general, the diffusion limit of oxygen is approximately 100 μm , which requires that all mammalian cells be located within 100-200 μm of blood vessels (294). Without a blood supply, tumors must depend solely on diffusion for oxygen and nutrients, which results in their maintaining a size of less than 1 mm in diameter in order to survive (64). Thus, the cancer cells in microscopic solitary tumors without angiogenesis generally remain dormant and occult for long periods of time. Only angiogenic macroscopic primary tumors and metastases are clinically detectable (64).

Factors responsible for angiogenesis include VEGF,

interleukin-8 (IL-8), PDGF, basic fibroblast growth factor (bFGF), the angiopoietin/Tie2 receptor complex, angiogenin, insulin-like growth factor (IGF), IGF-binding protein 1 (IGFBP-1), CXC chemokine receptor 4 (CXCR4) and its ligand CXCL12 (129,295,296). IL-8 and VEGF are the two most potent tumor-derived angiogenic factors (297-300).

VEGF as an angiogenic factor

VEGF expression participates in carcinogenesis (210,278,290,301-305). For human cancer, VEGF is the most important pro-angiogenic factor (293). In a study which examined the immunoexpression of VEGF in CIN, it was found that a progressive increase in VEGF immunoexpression was present as the tumor grade intensified (306). VEGF was distinguished by its being induced by either hypoxia or glucose deficiency (307,308). In solid tumors, some cancer cells expand outside the area of oxygen diffusion during tumor growth and become hypoxic, resulting in upregulation of VEGF and thus the occurrence of angiogenesis (309). After exposure to hypoxia for a few hours, different cell cultures showed dramatically increased VEGF messenger RNA levels which returned to background levels when a normal oxygen supply was resumed. Moreover, the production of VEGF was specifically induced by immediate proximity to necrotic tumor foci (307). Hypoxia inducible factor-1 (HIF-1) is considered a crucial mediator for the cellular response to hypoxia (309).

IL-8 as an angiogenic factor

HIF-independent mechanisms for angiogenesis have been described which involve a number of other molecules and transcription factors (309). IL-8 can be activated to preserve the tumor angiogenic response when VEGF production is suppressed. In HIF-1 α knockdown DLD-1 colon cancer cells, induction of IL-8 was also found to preserve the angiogenic response. Moreover, an antibody that neutralized IL-8 substantially inhibited angiogenesis and tumor growth in HIF-knock down DLD-1 but not in wild type DLD-1 xenografts (310). These studies suggest a compensatory angiogenic role for IL-8 when VEGF production is suppressed.

IL-8, in addition to being a tumor-derived pro-angiogenic factor, is also a proinflammatory chemokine which can be induced by thrombin, HPV infection,

pseudomonas or chlamydia trachomatis, gastric inflammation, or by chemical substances like palmitic acid, IL-1 β , eicosapentaenoic acid, or tumor necrosis factor- α (TNF α) (311-323). Turpin *et al.* reported that thrombin may drive tumorigenesis in colitis-associated colon cancer (324). Zhong *et al.* reported that thrombin promoted IL-8 secretion, epithelial ovarian cancer cell invasion and induction of epithelial-mesenchymal transition (325). The leading cause of cervical cancer is latent infection by oncogenic HPV. In culture cell lines positive for HPV-16 oncoproteins, the expression of angiogenic modulators, which includes pro-angiogenic molecules such as bFGF, IL-8, transforming growth factor, TNF α , and VEGF, was higher in these cells when compared to control keratinocytes (326). Also, overexpression of HPV-16 E6 and E7 oncoproteins in non-small cell lung cancer cells from never-smokers significantly promoted angiogenesis and an enhanced expression of HIF-1 α , VEGF, and IL-8 (327). These studies support the hypothesis that IL-8's pro-inflammatory effect may also contribute to angiogenesis.

LPA and angiogenic factors

LPA may contribute to angiogenic homeostasis by producing angiogenic factors (328). The most important LPA down-stream angiogenic factors are VEGF and IL-8. The other LPA-downstream factor is epidermal growth factor receptor (EGFR), whose pathway may also be linked with VEGF-directed angiogenesis (329). LPA may transactivate EGFR expression in ovarian, colon or prostate cancers (212,330,331). In cervical malignancy, EGFR was expressed abnormally when compared with normal squamous epithelium (332). However, for a number of epidermal cancers upregulation of EGFR was primarily associated with tumor cell growth due to uncontrollable division of cancer cells, not angiogenesis (333-340).

LPA and VEGF

LPA may induce VEGF expression in cancer cells (210,218,273,288,301-305,341-348). This finding is usually based on studies concerned primarily with ovarian cancer cells (210,301-304,342,343,345), and less frequently with studies of prostate cancer cells (278,305), colon cancer cells (344) or lung cancer cells (346). In ovarian cancer cells, besides hypoxia LPA may induce VEGF expression and stimulate ovarian tumor growth, migration, and invasion through transcriptional activation (210,273,286,290,301-

304,343,345). In fact, treating ovarian cancer cells with LPA resulted in VEGF protein levels that were elevated 1.5-fold in SKOV-3 cells, 1.9-fold in CAOV-3 cells, and threefold in OVCAR-3 cells (302). All the Edg-family LPA receptors—LPA1, LPA2, and LPA3—were detected in ovarian cancer cells; however, only LPA2 and LPA3 were found to play a role in LPA's stimulation of ovarian tumor growth (273,302). In contrast to the observation that most ovarian cancer cells express elevated levels of LPA2 and LPA3 mRNA and variable levels of LPA1 mRNA, normal ovarian epithelial cells were found to express LPA1 mRNA but to have low levels of LPA2 and LPA3 mRNA (349). These findings—that the expression of LPA2 or LPA3 during ovarian carcinogenesis contributed to ovarian cancer aggressiveness—suggest that the targeting of LPA production and action may possess potential for the treatment of ovarian cancer (273).

LPA and IL8

In ovarian cancer cells, besides VEGF LPA may also induce IL-8 secretion (286,348,350,351). Knockdown of either LPA2 or LPA3 receptors inhibited the production of IL-6, IL-8, and VEGF in SKOV-3 and OVCAR-3 cells (273). IL-8 has also been identified as an LPA-regulated factor in ovarian cancer cells and, through its up-regulation, as a contributor to cancer development and progression (286,350).

LPA may also induce secretion of both VEGF and IL-8 proteins in colon cancer cells. However, LPA was found to induce the secretion of more IL-8 than VEGF (352). In colon cancer DLD1 cells, Shida *et al.* found that LPA induced a dose-dependent increase in the secretion of both IL-8 (19-fold increase at 20 μ M) and VEGF (1.4-fold increase at 20 μ M). LPA, at concentrations that are present physiologically, enhanced DLD1 cell migration, proliferation, and adhesion, along with enhancing the secretion of angiogenic factors, all of which are crucial for cancer metastasis (352).

In cervical cancer, it was reported that LPA induced IL-8 secretion, angiogenesis, and tumor growth. VEGF levels induced by LPA receptor expression were quite low. LPA/IL-8 signaling was mediated through activation of LPA2 and LPA3 through the Gi/nuclear factor- κ B (NF- κ B) pathway (72).

For other angiogenic factors, that LPA induces their expression in human cancer cells has been reported rarely. For example, in one study LPA did not significantly alter

matrix metalloproteinase 2 secretion or activation in DLD1 cells (352). On the other hand, most ovarian cancer cell lines, including OVCAR-3, Caov-3, and SKOV-3, do not seem to express functional levels of PDGF receptors (353). PDGF and bFGF do not seem connected with angiogenesis due to LPA receptor over-expression (72).

Targeted therapy of angiogenic factors

The clinical use of angiogenesis inhibitors may be a promising direction in pharmacological research (43,293). For advanced and recurrent cervical cancer, targeted agent therapy, alone or combined with chemotherapy, has been under evaluation and shows promise. Several LPA receptor analogues and small molecules which target LPA receptors have been discovered which were found to be efficacious in attenuating tumor pathology (354,355). Agents targeting VEGF and EGFR signaling pathways are the most investigated molecular targeting agents for cervical cancer (355). However, EGFR inhibitors have not shown promise (41).

VEGF as an anti-angiogenic target

Currently, VEGF and its receptors are the only targets used in anti-angiogenesis therapy (356). For advanced cervical cancer, in 2014 a prospective randomized Phase III clinical trial (GOG 240) which explored the impact of adding the antiangiogenic agent bevacizumab to a combination of cisplatin and either paclitaxel or topotecan showed a small but significant therapeutic benefit of 3.7 months added to median OS without significant deterioration in health-related quality of life (357,358). Bevacizumab, a monoclonal antibody for VEGF, was associated with an increased incidence of hypertension, thromboembolic events, and gastrointestinal fistula when compared with chemotherapy alone. On August 14, 2014, the US Food and Drug Administration approved bevacizumab for the treatment of persistent, recurrent, and metastatic cervical cancer when used in combination with other chemotherapeutic agents (cisplatin-paclitaxel-bevacizumab or topotecan-paclitaxel-bevacizumab regimens) (357,359).

However, in general the clinical effects of antiangiogenic agents may easily cause drug resistance, and thus their usefulness is usually transient (360). For most tumors, anti-angiogenesis treatments targeting VEGF had only a limited OS benefit compared with conventional chemotherapy alone; moreover, these treatments tended to

induce resistance and tumor cell invasion by selecting for highly invasive tumor cells or hypoxia-resistant cells (361). Specifically, intrinsic resistance has also been associated with bevacizumab (362,363). Although the GOG 240 clinical trial report on bevacizumab has encouraged its use for advanced cervical cancer treatment, in view of its high cost, limited OS benefit, and rapid induction of resistance, further exploration and evaluation of anti-angiogenic agents must be taken into consideration (41,363-367). Moreover, in a study to determine whether markers of tumor angiogenesis were associated with cervical cancer survival, high CD31 MVD but not VEGF was found to be an independent prognostic factor for progression-free survival (PFS) and OS (62).

The other VEGF-directed multi-targeted anti-angiogenic tyrosine kinase inhibitors such as cediranib and pazopanib have shown some therapeutic benefits in ovarian cancer, with both resulting in improvements in PFS and OS (39). However, prospects for their use as treatments for cervical cancer remain uncertain (366). The usefulness of novel anti-angiogenic agents thus merits further investigation.

IL-8 as an anti-angiogenic target

LPA may promote angiogenesis in both normal and cancer cells via up-regulation of IL-8. *Table 2* lists reports that simultaneously investigate both angiogenesis and LPA-induced IL-8 up-regulation.

LPA treatment increased the angiogenic capability of cultured chondrocytes and resulted in enhanced capillary tube formation, monolayer permeability, migration, and cell growth in human umbilical vein endothelial cells (HUVECs). Angiogenin, IGFBP-1, IL-8, monocyte chemoattractant protein 1 (MCP-1), matrix metalloproteinase 9, and VEGF mRNA protein expression were significantly enhanced in LPA-treated chondrocytes. LPA2, 3, 4 and 6 were expressed in chondrocytes (296).

In cervical cancer, all three Edg receptors are expressed in cervical cancer cells. A study of the LPA receptor signaling cascade that used a mice model showed for the first time that knocking out the receptors LPA2 and LPA3, but not LPA1, decreased cervical cancer tumor growth and tumor MVD (72). Priming cervical cancer cells with LPA increased angiogenesis, as was shown by endothelial growth via HUVEC assay, and by endothelial migration via permeability assays. In cell cultures, knocking out the receptors LPA2 and LPA3 also inhibited angiogenesis,

whereas cell proliferation was not influenced by knocking down any two or all the three Edg-family receptors. This study revealed that LPA may promote angiogenesis, and that angiogenic suppression that blocks the receptors LPA2 and LPA3 may inhibit tumor growth *in vivo* (72). Overall, in cervical cancer cells the most important LPA-related angiogenic factor was IL-8.

In first-trimester placental trophoblasts, the primary LPA receptor is LPA1. LPA enhanced growth-regulated oncogene— α , IL-8 and MCP-1 expression in a time- and dose-dependent manner (222).

In breast cancer cell lines (Hs 578T, MCF-7, MDA-MB-231, MDA-MB-435S, SK-BR-3, T-47D, and ZR-75-1 cells), sphingosine-1-phosphate (S1P), but not LPA, controlled the expression of VEGF. LPA and S1P had indirect angiogenic properties, as was shown by induced secretion of angiogenic factors by breast cancer cells primed with these LPLs (341).

LPA mediates IL-8 expression in human endometrial stromal cells through its LPA receptors. In endometrial specimens obtained from 38 premenopausal women undergoing hysterectomy for leiomyoma, and in decidua or placenta specimens that were obtained from 12 women who had received an elective termination of pregnancy, LPA enhanced IL-8 expression in a dose- and time-dependent manner and enhanced capillary tube formation and proliferation of human endometrial microvascular endothelial cells (224). Through the LPA1 receptor, LPA induced IL-8 expression and thus may have played a role in the angiogenesis of the endometrium and placenta (224).

In ovarian cancer cells, Fang *et al.* found that LPA induced expression of IL-8 mRNA mainly through transcriptional activation. Using IL-8 gene promoter luciferase assays in which cell lines were transfected with the plasmid pIL-8-Luc, they confirmed that LPA activates the IL-8 gene promoter in ovarian cancer cells. By contrast, in the control there was only a limited increase in luciferase activity in OVCAR-3 cells transfected with pGL2-Luc. The LPA2 receptor was identified as the one that most efficiently linked LPA to IL-6 and IL-8 production (286).

In *in vitro* ovarian cancer cells (HEY, OCC1, and SKOV3), Schwartz *et al.* found that LPA at concentrations of 5-15 μ M induced increases in mRNA levels (2- to 7-fold increase) and in protein secretion (2- to 12-fold increase) of IL-8. In a breast cancer cell line, MCF7 cells responded to LPA by increasing the secretion of IL-8. LPA was found to regulate the mRNA and protein levels of the proinflammatory and proangiogenic factor IL-8 in ovarian

Table 2 Selected references on lysophosphatidic acid (LPA) induction of interleukin-8 (IL-8) secretion and angiogenesis

Authors	Cell types	Angiogenic LPA receptors	Findings	Comments	Reference
Chen et al. (2012)	Cervical cancer cells (SiHa, HeLa and CaSki cells)	LPA2, LPA3	LPA2 and LPA3 are crucial for angiogenesis in both cultured cells and receptor knockout mice	The most important angiogenic factor is IL-8, not VEGF, bFGF, PDGF, or IL-6	(72)
Chen et al. (2010)	First-trimester trophoblasts	LPA1	LPA-induced IL-8 chemokine production of trophoblasts enhanced permeability, migration, proliferation, and capillary tube formation in human endometrial microvascular endothelial cells	Through secretion of LPA-induced IL-8, first-trimester human trophoblast cells may regulate angiogenesis in early pregnancy	(222)
Chen et al. (2008)	Granulosa-lutein cells	LPA1, LPA2, LPA3	LPA-induced IL-8 and IL-6 increased the permeability of the human umbilical vein endothelial cell monolayer	LPA's induction of IL-8 in preovulatory follicles may play a role in the angiogenesis of the corpus luteum	(223)
Chen et al. (2008)	Endometrial and decidual or placental cells	LPA1	LPA-induced IL-8 enhanced migration, permeability, capillary tube formation, and proliferation of human endometrial microvascular endothelial cells. Through the LPA1 receptor, LPA induces IL-8 expression via a NF- κ B-dependent signal pathway	LPA enhanced IL-8 expression in a dose- and time-dependent manner. LPA may play a role in the angiogenesis of the endometrium and placenta via LPA1	(224)
Fang et al. (2004)	Ovarian cancer cells (OVCAR-3, SKOV-3, and DOV-13)	LPA2	After using luciferase assays to characterize the IL-8 gene promoter in ovarian cancer cells, this study confirmed that LPA induces transcriptional activation of the IL-8 gene. This finding suggests that LPA represents a major regulator of IL-8 expression <i>in vivo</i>	LPA is a potent inducer of IL-6 and IL-8 production	(286)
Chuang et al. (2014)	Chondrocytes (CHON-001 and HC)	LPA2, LPA3, LPA4, LPA6	LPA treatment promoted angiogenesis unequally in enhanced angiogenin, IGFBP-1, IL-8, MCP-1, MMP-9, and VEGF mRNA and protein expression	Among the angiogenic proteins, IL-8 possesses the highest fold of increase	(296)
Boucharaba et al. (2009)	Human breast cancer cells (MDA-BO21, Hs 578T, MCF-7, MDA-MB-231, MDA-MB-435S, SK-BR-3, T-47D, and ZR-75-1 cells)	LPA2	LPA and SIP act directly on endothelial cells to induce angiogenesis. LPA and SIP were proven to have indirect angiogenic properties, as shown by the induced secretion of angiogenic factors by breast cancer cells primed with these lysophospholipids	LPA induced secretion of IL-8. LPA does not appear to control the expression of VEGF-A in breast cancer cells	(341)
Schwartz et al. (2001)	Ovarian cancer cells (HEY, OCC1, and SKOV3) and breast cancer cells (MCF7 cells)	Not reported	LPA increased IL-8 mRNA levels and protein secretion of IL-8 in ovarian cancer cells <i>in vitro</i> . These results were both dose- and time-dependent. MCF7 cells responded to LPA by increasing the secretion of IL-8	LPA regulates the mRNA and protein levels of the proinflammatory and proangiogenic factor IL-8 in ovarian cancer cells	(350)
Shida et al. (2003)	Human colon carcinoma cells (DLD1, HT29 and WiDR)	LPA1 (DLD1), LPA2 (HT29 and WiDR)	LPA induced secretion of both VEGF and IL-8 proteins. LPA induced NF- κ B activation and subsequent secretion of IL-8 in colon cancer	LPA induced significant secretion of IL-8 and VEGF. IL-8 secretion was much greater than VEGF secretion	(352)
Lu et al. (2002)	Ovarian cancer cells (HEY and SKOV3)	Possibly by Edg receptors (LPA1, LPA2, LPA3)	Naturally occurring alkyl- and alkenyl-lysophosphatidic acids induced cell migration and the secretion of a pro-angiogenic factor, IL-8	Lysophosphatidic acids induced IL-8 secretion. This study suggests that LPA is potentially related to tumor metastasis and angiogenesis	(368)

VEGF, vascular endothelial growth factor; NF- κ B, nuclear factor- κ B.

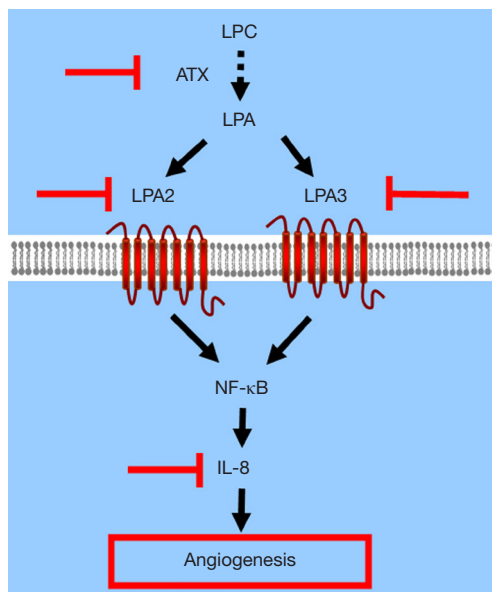


Figure 1 Schematic representation of ATX/LPA/IL-8 signaling and possible targeting sites for cervical cancer angiogenesis. Red bar: inhibition. LPC, lysophosphatidylcholine; ATX, autotaxin; LPA, lysophosphatidic acid; LPA2, LPA receptor type 2; LPA3, LPA receptor type 3; NF- κ B, nuclear factor- κ B; IL-8, interleukin-8.

cancer cells (350).

In cultured granulosa-lutein cells, LPA-induced IL-8 mediated tube formation in HUVEC assay, which suggests that in preovulatory follicles LPA may play a role in the angiogenesis of corpus luteum (223).

Additionally, in ovarian cancer cells LPA induced cell migration and the secretion of IL-8, a pro-angiogenic factor (368). This study suggests that LPA is potentially related to both tumor metastasis and angiogenesis. Also, it found that Al-LPAs induced diverse signaling pathways in ovarian cancer cells.

Overall, LPA may induce angiogenesis mediated by IL-8 in normal or cancer cells. In cervical cancer, IL-8 is the most important, if not the exclusive, mediator. Targeting the LPA/IL-8 axis may thus be a promising pharmacological approach for cervical cancer treatment.

Conclusions

Because of recent advances in cervical cancer prevention by HPV vaccination, better screening and earlier treatment for CIN, and more aggressive management of invasive

cancer, cervical cancer has become more preventable and treatable. However, its incidence and mortality remain high. For metastatic or recurrent disease, targeted molecular translation may be either an alternative to cytotoxic chemotherapy or an additional treatment. Angiogenesis has a clinical, pathological and molecular meaning for cervical carcinoma. Bevacizumab, a recombinant humanized monoclonal antibody which binds with the angiogenic factor VEGF, has been demonstrated to have a significant clinical effect, with 3.7 months of OS improvement for cervical cancer patients. The ATX-LPA-IL-8 axis signaling cascade may also have potential for the anti-angiogenic treatment of cervical cancer (*Figure 1*). Molecular therapy that targets this pathway may improve the prognosis of patients with advanced cervical cancer, and thus merits further investigation.

Acknowledgments

Funding: This work was supported by the National Science Council, Grant number 102-2314-B-002-110-MY2, and by National Taiwan University Hospital, Grant numbers ME-109 and MG-164.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Cancer Research* for the series “Lysophospholipids on Immunity and Cancer”. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.3978/j.issn.2218-676X.2015.10.09>). The series “Lysophospholipids on Immunity and Cancer” was commissioned by the editorial office without any funding or sponsorship. HL served as the unpaid Guest Editor of the series. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Chen RJ, Chou CH, Chen SU, Lee H. Angiogenic effect of lysophosphatidic acid receptors on cervical cancer cells. *Transl Cancer Res* 2015;4(5):500-526. doi: 10.3978/j.issn.2218-676X.2015.10.09