Lysophosphatidic Acid and Cancer

Subjects: Oncology | Biochemistry & Molecular Biology | Chemistry, Medicinal
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Lysophosphatidic acid (LPA) is a bioactive lipid mediator primarily derived from membrane phospholipids. LPA initiates cellular effects upon binding to a family of G protein-coupled receptors, termed LPA receptors (LPAR1 to LPAR6). LPA signaling drives cell migration and proliferation, cytokine production, thrombosis, fibrosis, angiogenesis, and lymphangiogenesis.

Keywords: antagonist ; cancer ; clinical trial ; lysophosphatidic acid ; lysophosphatidic receptor ; therapy

1. Overview

Lysophosphatidic acid (LPA) is a bioactive lipid mediator primarily derived from membrane phospholipids. LPA initiates cellular effects upon binding to a family of G protein-coupled receptors, termed LPA receptors (LPAR1 to LPAR6). LPA signaling drives cell migration and proliferation, cytokine production, thrombosis, fibrosis, angiogenesis, and lymphangiogenesis. Since the expression and function of LPA receptors are critical for cellular effects, selective antagonists may represent a potential treatment for a broad range of illnesses, such as cardiovascular diseases, idiopathic pulmonary fibrosis, voiding dysfunctions, and various types of cancers. More new LPA receptor antagonists have shown their therapeutic potentials, although most are still in the preclinical trial stage. This review provided integrative information and summarized preclinical findings and recent clinical trials of different LPA receptor antagonists in cancer progression and resistance. Targeting LPA receptors can have potential applications in clinical patients with various diseases, including cancer.

2. Lysophosphatidic Acid

Lysophosphatidic acid (LPA) and LPA receptors (LPARs), including LPAR1 to LPAR6, are integral parts of signaling pathways involved in cellular proliferation/migration/survival, vascular homeostasis, stromal remodeling, lymphocytes trafficking, and immune regulation [1][2][3]. In addition, autotaxin (ATX) is a secreted glycoprotein and functions as a pivotal enzyme to produce extracellular LPA [4][5]. Figure 1 illustrates the extracellular and intracellular biosynthesis of LPA. Consequently, aberrant ATX-LPA-LPAR axis may be involved in the development and progression of many pathologic conditions such as cancer and metastasis [6][7], radio- and chemo-resistances [8][9][10][11][12], fibrotic diseases [13], neuropathic pain [14], arthritis [15], metabolic syndromes [16], and atherosclerosis [17]. Understanding ATX/LPA expression and LPAR-mediated signals elucidated our understanding of the disease mechanisms and highlighted the therapeutic potential of the druggable ATX-LPAR axis. To date, enormous in vivo and in vitro investigations have demonstrated pharmacological antagonization of LPAR to be of paramount significance in reversing pathologic responses. This article sought to update current progress regarding LPAR antagonists in clinical and preclinical settings, emphasizing compounds being evaluated in completed and ongoing clinical trials.

3. LPA Receptor-Mediated Signaling in Cancer Biology

ATX-LPA-LPAR signaling is a complex network and intertwines with multiple cellular signaling to contribute a plethora of activities such as proliferation, survival, migration, metastasis, angiogenesis, and inflammation in cancers [6]. Individual LPARs favor different Gα proteins for their downstream signals and cellular functions. In brief, the endothelial cell differentiation gene (EGD) family LPARs (LPAR1 to LPAR3) bind to $G_{i/o}$ and trigger the *Ras/Raf/MAPK* signaling pathway, phospholipase C (PLC), and the PI3K-Akt pathway [1][3][18][19]. $G_{q/11}$ protein couples LPAR1–5 to mediate PLC and calcium mobilization [20], whereas $G_{12/13}$ interacts with all LPARs, leading to cell migration and invasion through Rho and *Rho*-associated protein kinase (*ROCK*) activation [21]. Signaling through Gs would activate the cAMP-dependent protein kinase A (PKA) signaling pathway and the large tumor suppressor 1 and 2 (*LATS1/2*). It would subsequently inhibit downstream transcriptional co-activators Yes-associated protein (YAP) and PDZ-binding motif (TAZ), which usually drive

cancer cell survival, proliferation, invasive migration, and metastasis [22][23]. Interestingly, the *ROCK* activation would suppress LATS1/2 and subsequently activate YAP and TAZ, resulting in tumorigenesis (Figure 2).

The LPA-LPAR signaling pathway is one of the most investigated mechanisms because overexpression of one or more of these receptors was found in several types of cancers. Therefore, the concept of modulating cancer by agonizing or antagonizing LPARs is naturally generated. The following sessions would discuss all LPARs in detail.

3.1. LPAR 1

Studies show that LPAR1 enhances metastasis and tumor motility [18]. Aberrant LPAR1 expressions were observed in many cancer cell lines and primary tumors, including ovarian cancer [24], breast cancer [25], liver cancer [26], gastric cancer [27], pancreatic cancer [28][29], lung cancer [30][31], glioblastoma (GBM) [32][33][34], and osteosarcoma [35]. Ovarian cancer is the most investigated cancer in studying the malignancy of LPA signaling. High LPAR1 expressions in ovarian serous cystadenocarcinoma correlate with high proliferation, invasion, migration, and poorer prognosis than those with low expressions [36]. LPAR1 also promotes the development of intratumoral heterogeneity by regulating PI3K/AKT signaling [36]. Retaining the stemness phenotype of ovarian cancer, an autocrine loop via the ATX-LPA-LPAR1-AKT1 signaling axis is critical [37]. In breast cancer, overexpression of LPAR1 in MCF-10A mammary epithelial cells causes cells to acquire an invasive phenotype [38], which correlates with the heparin-binding EGF-like growth factor [39] and mediate basal breast metastasis through LPAR1-PI3K-ZEB1-miR-21 pathways [25]. For hepatocellular carcinoma, LPA-LPAR1 enhances cancer invasion via inducing MMP-9 expression through coordinate activation of PI3K and p38 MAPK signaling cascade [26]. Similarly, increased cancer cell invasiveness mediated by LPAR1 was found in pancreatic cancer [28][29]. For lung A549 cancer cells, the LPAR1/Gi/MAP kinase/NF-κB pathway is involved in LPA-induced oncogenesis, and using the LPAR1/3 antagonist Ki16425 to block LPAR1-mediated signaling would significantly reduce tumor volume [31]. In GBM, LPAR1 expression is also significantly higher than other gliomas [32]. Of interest, the LPA pathway of microglia-and-GBM interaction is a target to improve survival because microglia-derived LPA and ATX upon hypoxia stress may promote GBM proliferation and migration [32]. A recent report indicates LPAR1/PKCα/progesterone receptor pathway is involved in GBM migration [40]. In prostate PC-3 cancer cells, hyperglycemia triggers enhanced vascular endothelial growth factor-C (VEGF-C) expression via the LPAR1/3-Akt-ROS-LEDGF signaling [40]. The LPA-mediated VEGF-C expression can be modified by calreticulin, a multifunctional chaperon protein. In addition, pharmacological LPAR1 receptor antagonism may significantly reduce tumoral lymphatic vessel density and nodal metastasis in tumor-bearing nude mice, suggesting the key role of LPAR1 in prostate cancer lymphatic metastasis [41].

3.2. LPAR2

LPAR2 activation has been shown to associate with cell survival because of its anti-apoptosis function. For ovarian cancer, tumors with overexpression of LPAR2 were associated with poorer survivals compared with controls [42]. Furthermore, LPAR2 signaling promotes invasion and metastasis through the production of VEGF [43], EGFR [44], interleukin-8 [45], and urokinase plasminogen activation [46], implying the multiple hyper-vascularization processes. LPAR2-Gi-Src-EGFR-ERK signaling cascade may mediate cell movement and LPA-stimulated COX-2 expression [47]. Together with LPAR1, LPAR2 regulates phosphorylation of ezrin/radixin/moesin (ERM) proteins, known as membrane-cytoskeleton linkers, and leads to promotion of ovarian OVCAR-3 cancer cell migration through cytoskeletal reorganization and formation of membrane protrusions [48]. The metastatic activity of gastric SGC-7901 cells was enhanced as well through LPA-LPAR2-Notch pathway activation [27]. LPAR2 is the major LPAR in colon cancer, and most of the cellular signals by LPAR2 were primarily mediated through interaction with scaffold proteins Na^+/H^+ exchanger regulatory factor 2 (NHERF2) [49]. In another two reports, LPA-LPAR2 may facilitate colon cancer proliferation via transcription factor Kruppel-like factor 5 (KLF5) and hypoxia-inducible factor 1α (HIF-1α) activations. The LPAR2 associated HIF-1α expression also promoted breast cancer proliferation/migration and conferred poor prognosis in the Chinese population [50]. Regarding the link between chronic inflammation and cancer, Lin et al. found genetic LPAR2 depletion may attenuate colon cancer development in a colitis mice model triggered by azoxymethane and dextran sulfate sodium [51]. Noteworthy, LPAR2 activation may exert anti-migration effects by blocking EGF-induced migration and invasion of pancreatic Panc-1 cancer cells through the $G_{12/13}$/Rho signaling pathway [52]. G_{i2} protein is also involved in enhanced ovarian cancer invasion and migration via the HIF1α-LPA-LPAR2 axis [24]. The distinct structure of LPAR2 from other LPARs is its carboxyl-terminal tail contains a zinc finger-binding motif to interact with TRIP6 and pro-apoptotic Siva-1. TRIP6 has a PSD95/Dlg/ZO-1 (PDZ)-binding motif to interact with scaffold proteins, particularly NHERF2 [53]. Siva-1 is an early response gene activated by DNA damage that promotes apoptosis through binding up the antiapoptotic Bxl-XL protein. Moreover, Siva-1 acts with p53 and the ubiquitin ligase Mdm2 in the nucleus complexes, and the polyubiquitinated complex would be degraded once the LPA-LPAR2 axis is activated. The functional significance of the LPAR2-activated assembly leads to up-regulation of ERK1/2, PI3K-Akt, and NFκB prosurvival pathways and the subsequent inhibition of apoptosis [54]. LPAR2 can protect

cancer cells against apoptotic stress after irradiation and chemotherapy by augmenting DNA damage repair response and inhibiting the mitochondrial apoptosis cascade [55].

3.3. LPAR3

LPAR3 is the predominant receptor subtype in colon, liver, and lung cancers. LPAR3-expressing cells significantly promote motility and invasiveness through Ras-, Rac-, Rho-, and PI3K-signaling pathways [20]. In hepatocellular carcinoma, Zuckerman et al. reported distinct LPAR3 expressions within the tumor and normal tissues, and LPAR3 may enhance liver cancer migration via the LPAR3-Gi-ERK/MAPK pathway [56]. Okabe et al. found LPAR3 contributes to hepatocellular carcinoma proliferation and invasion via the β-catenin pathway in rat hepatic RH7777 cancer cells. They also demonstrated that tumor cells with high LPAR3 expression were resistant to cisplatin and doxorubicin through multidrug-resistance-related up-regulation of genes [20]. In melanoma, LPAR3 is essential to promote viability and proliferation, and the Src homology 3 domain is required for LPAR3 to mediate viability in melanoma SK-MEL-2 cells [57] [58]. In ovarian cancer, LPAR3 promotes cell expansion and invasion in SKOV-3 cells, and tumors with overexpression of LPAR3 were associated with poor survival [42]. Besides G_q and G_i proteins, LPAR3 can also activate $G_{12/13}$, increase dephosphorylation and nuclear translocation of YAP, and induce migration of ovarian cancer cells [59]. In addition, the LPA/LPAR3 signaling may initiate mutation-independent epithelial-to-mesenchymal transition (EMT) through β1-integrin-dependent activation of Wnt/β-catenin signaling [60]. Pharmacological suppression of LPAR3 would suppress motility and invasion in various cancers, including hamster pancreatic cancer cells [61], human triple-negative breast cancers [62], fibrosarcoma HT1080 cells, and osteosarcoma HOS cells [63]. Direct targeting of LPAR3 by miR-15b has been shown to repress cell proliferation and drive the senescence and apoptosis of ovarian cancer cells through the PI3K/Akt pathway [64], suggesting the potential mRNA treatment against LPAR3.

3.4. LPAR4

In contrast to LPAR1–3, LPAR4 and LPAR5 negatively affected cancer cell proliferation and motility [65]. LPAR4 attenuates tumor motility and colony formation in colon cancer cell lines. Knockdown of LPAR4 in the long-term 5FU treated DLD1 cells increased cell motility [66][67]. Similarly, LPAR4 depletion increases tumor motility in pancreatic cancer cells [65] and increases tumor proliferation in head and neck carcinoma [68]. Another recent study by Eino et al. found that LPAR4 is critical for developing a fine capillary network in brain tumors [69]. LPAR4 promotes endothelial cell-cell adhesion and VCAM-1 expression via RhoA/ROCK signaling, enhancing anti-PD1 therapy efficacy and lymphocyte infiltration [69]. However, a contradictory pro-tumorigenesis was found in fibrosarcoma. In HT1080 cells, LPAR4 promotes cell invasion and invadopodium formation via cAMP/EPAC/Rac1 signaling [70]. Of interest, LPAR4/6 is necessary for embryogenic angiogenesis to activate YAP and transcriptional coactivator TAZ via the G_{12}/G_{13} signaling pathway [71]. In the malignancies, YAP promotes cancer proliferation and migration in bladder cancers through YAP-Mask2 [72] and lung cancers through LKB1-YAP-human telomerase RAN (hTERC), respectively [73]. These suggested the involvement of LPAR4 in YAP-mediated cancer progression.

3.5. LPAR5

LPAR5 was considered a negative regulator in cancer cell motility and survival [69]. The inhibitory effect of LPAR5 on cell motility has been shown in pancreatic cancer [69] and sarcoma [74]. Nevertheless, contradictory effects of LPAR5 were found in different cancers. Okabe et al. reported upregulation of the *LPAR5* gene with aberrant unmethylated status enhanced cell proliferation and motility in rat liver-derived hepatoma RH7777 and lung-derived adenocarcinoma RLCNR cells [75]. Blocking LPAR5 in thyroid cancer with a selective LPA5 antagonist TCLPA5 attenuated cancer proliferation and migration via PI3K/Akt signaling in vivo and in vitro [76]. Moreover, depletion of LPAR5 in murine B16-F10 melanoma resulted in fewer lung metastasis [77]. Interestingly, LPAR5 appears to mediate chemorepulsion in response to LPA. The underlying mechanism was proposed to be mediated via a non-canonical elevation of cAMP along with reduced PIP3 signaling in melanoma B16 cells [78]. LPAR5 expression is markedly increased in long-term cisplatin-treated melanoma cells [8]. Therefore, LPAR5 knockdown significantly conferred chemo-resistance and enhanced cancer cell survival [8]. In addition to the cancer cell growth and metastasis, LPAR5 was shown to suppress the function of CD8-positive cytotoxic T cells by inhibiting intracellular Ca^{2+} mobilization and ERK activation, suggesting LPAR5 might act as a mediator of immune suppression [79].

3.6. LPAR6

Reports regarding LPAR6 in cancer are relatively limited compared with other LPARs [2]. Several articles investigated the role of LPAR6 in liver, pancreatic, and colon cancers. LPAR6 expression in hepatocellular carcinoma correlated with poorer survival [80] and increased microvascular invasion [81]. Moreover, LPAR6 promotes hepatocellular carcinoma

proliferation via the NCOA3-LPAR6-HGF signaling cascade, and the tumor-suppressive effect by depletion of LPAR6 is similar to that of anti-HGF treatment [82]. In pancreatic cancer, LPAR6 knockdown also inhibited cancer invasion and colony formation [67]. However, LPAR6 can, by contrast, be a negative regulator in different cancers. LPAR6 knockdown caused larger colonies [83] and enhanced motility in colon DLD1 and HCT116 cancer cells [67]. The role of LPAR6 in various cancer types should be further characterized in the future.

4. Conclusions

In conclusion, it deserves our attention that multiple therapeutic agents undergo clinical trials or preclinical evaluation for various diseases via inhibition of LPA signaling. Their safety is generally acceptable, and the LPAR antagonists are potentially effective and novel for improving pain and current cancer therapies. In general, being inflammatory mediators, LPA signaling inhibitors could be potential therapeutic modalities for chemoprevention, enhancing the efficacy of chemotherapy and radiotherapy and improving prognosis.

References

1. Choi, J.W.; Herr, D.R.; Noguchi, K.; Yung, Y.C.; Lee, C.W.; Mutoh, T.; Lin, M.E.; Teo, S.T.; Park, K.E.; Mosley, A.N.; et al. LPA receptors: Subtypes and biological actions. Annu. Rev. Pharmacol. Toxicol. 2010, 50, 157–186.
2. Taniguchi, R.; Inoue, A.; Sayama, M.; Uwamizu, A.; Yamashita, K.; Hirata, K.; Yoshida, M.; Tanaka, Y.; Kato, H.E.; Nakada-Nakura, Y.; et al. Structural insights into ligand recognition by the lysophosphatidic acid receptor LPA6. Nature 2017, 548, 356–360.
3. Geraldo, L.; Spohr, T.; Amaral, R.; Fonseca, A.; Garcia, C.; Mendes, F.A.; Freitas, C.; Fabio dosSantos, M.; Lima, F. Role of lysophosphatidic acid and its receptors in health and disease: Novel therapeutic strategies. Signal Transduct. Target Ther. 2021, 6, 45.
4. Zhang, X.; Li, M.; Yin, N.; Zhang, J. The expression regulation and biological function of autotaxin. Cells 2021, 10, 939.
5. Gellett, A.M.; Kharel, Y.; Sunkara, M.; Morris, A.J.; Lynch, K.R. Biosynthesis of alkyl lysophosphatidic acid by diacylglycerol kinases. Biochem. Biophys. Res. Commun. 2012, 422, 758–763.
6. Gotoh, M.; Fujiwara, Y.; Yue, J.; Liu, J.; Lee, S.; Fells, J.; Uchiyama, A.; Murakami-Murofushi, K.; Kennel, S.; Wall, J.; et al. Controlling cancer through the autotaxin-lysophosphatidic acid receptor axis. Biochem. Soc. Trans. 2012, 40, 31–36.
7. Benesch, M.; MacIntyre, I.; McMullen, T.; Brindley, D.N. Coming of age for autotaxin and lysophosphatidate signaling: Clinical applications for preventing, detecting and targeting tumor-promoting inflammation. Cancers 2018, 10, 73.
8. Minami, K.; Ueda, N.; Maeda, H.; Ishimoto, K.; Otagaki, S.; Tsujiuchi, T. Modulation of chemoresistance by lysophosphatidic acid (LPA) signaling through LPA5 in melanoma cells treated with anticancer drugs. Biochem. Biophys. Res. Commun. 2019, 517, 359–363.
9. Ishimoto, K.; Minami, A.; Minami, K.; Ueda, N.; Tsujiuchi, T. Different effects of lysophosphatidic acid receptor-2 (LPA2) and LPA5 on the regulation of chemoresistance in colon cancer cells. J. Recept. Signal Transduct. Res. 2021, 41, 93–98.
10. Ueda, N.; Minami, K.; Ishimoto, K.; Tsujiuchi, T. Effects of lysophosphatidic acid (LPA) receptor-2 (LPA2) and LPA3 on the regulation of chemoresistance to anticancer drug in lung cancer cells. Cell Signal. 2020, 69, 109551.
11. Minami, K.; Ueda, N.; Ishimoto, K.; Tsujiuchi, T. Lysophosphatidic acid receptor-2 (LPA2)-mediated signaling enhances chemoresistance in melanoma cells treated with anticancer drugs. Mol. Cell. Biochem. 2020, 469, 89–95.
12. Minami, K.; Ueda, N.; Ishimoto, K.; Kurisu, R.; Takamoto, M.; Ikeda, H.; Tsujiuchi, T. Cooperation of G12/13 and Gi proteins via lysophosphatidic acid receptor-2 (LPA2) signaling enhances cancer cell survival to cisplatin. Biochem. Biophys. Res. Commun. 2020, 532, 427–432.
13. Radhakrishnan, R.; Ha, J.H.; Jayaraman, M.; Liu, J.; Moxley, K.M.; Isidoro, C.; Sood, A.K.; Song, Y.S.; Dhanasekaran, D.N. Ovarian cancer cell-derived lysophosphatidic acid induces glycolytic shift and cancer-associated fibroblast-phenotype in normal and peritumoral fibroblasts. Cancer Lett. 2019, 442, 464–474.
14. Uchida, H.; Nagai, J.; Ueda, H. Lysophosphatidic acid and its receptors LPA1 and LPA3 mediate paclitaxel-induced neuropathic pain in mice. Mol. Pain 2014, 10, 71.
15. Orosa, B.; García, S.; Conde, C. The autotaxin-lysophosphatidic acid pathway in pathogenesis of rheumatoid arthritis. Eur. J. Pharmacol. 2015, 765, 228–233.

16. Kraemer, M.P.; Mao, G.; Hammill, C.; Yan, B.; Li, Y.; Onono, F.; Smyth, S.S.; Morris, A.J. Effects of diet and hyperlipidemia on levels and distribution of circulating lysophosphatidic acid. J. Lipid Res. 2019, 60, 1818–1828.

17. Zhou, Y.; Little, P.J.; Ta, H.T.; Xu, S.; Kamato, D. Lysophosphatidic acid and its receptors: Pharmacology and therapeutic potential in atherosclerosis and vascular disease. Pharmacol. Ther. 2019, 204, 107404.

18. Yung, Y.C.; Stoddard, N.C.; Chun, J. LPA receptor signaling: Pharmacology, physiology, and pathophysiology. J. Lipid Res. 2014, 55, 1192–1214.

19. Xu, Y. Targeting Lysophosphatidic Acid in Cancer: The issues in moving from bench to bedside. Cancers 2019, 11, 1523.

20. Okabe, K.; Hayashi, M.; Kato, K.; Okumura, M.; Fukui, R.; Honoki, K.; Fukushima, N.; Tsujiuchi, T. Lysophosphatidic acid receptor-3 increases tumorigenicity and aggressiveness of rat hepatoma RH7777 cells. Mol. Carcinog. 2013, 52, 247–254.

21. Lee, M.; Choi, S.; Halldén, G.; Yo, S.J.; Schichnes, D.; Aponte, G.W. P2Y5 is a G(alpha)i, G(alpha)12/13 G protein-coupled receptor activated by lysophosphatidic acid that reduces intestinal cell adhesion. Am. J. Physiol. Gastrointest. Liver Physiol. 2009, 297, G641–G654.

22. Rao, R.; Salloum, R.; Xin, M.; Lu, Q.R. The G protein Gαs acts as a tumor suppressor in sonic hedgehog signaling-driven tumorigenesis. Cell Cycle 2016, 15, 1325–1330.

23. Luo, J.; Yu, F.-X. GPCR-Hippo Signaling in Cancer. Cells 2019, 8, 426.

24. Ha, J.H.; Ward, J.D.; Radhakrishnan, R.; Jayaraman, M.; Song, Y.S.; Dhanasekaran, D.N. Lysophosphatidic acid stimulates epithelial to mesenchymal transition marker Slug/Snail2 in ovarian cancer cells via Gαi2, Src, and HIF1α signaling nexus. Oncotarget 2016, 7, 37664–37679.

25. Sahay, D.; Leblanc, R.; Grunewald, T.G.; Ambatipudi, S.; Ribeiro, J.; Clézardin, P.; Peyruchaud, O. The LPA1/ZEB1/miR-21-activation pathway regulates metastasis in basal breast cancer. Oncotarget 2015, 6, 20604–20620.

26. Park, S.Y.; Jeong, K.J.; Panupinthu, N.; Yu, S.; Lee, J.; Han, J.W.; Kim, J.M.; Lee, J.S.; Kang, J.; Park, C.G.; et al. Lysophosphatidic acid augments human hepatocellular carcinoma cell invasion through LPA1 receptor and MMP-9 expression. Oncogene 2011, 30, 1351–1359.

27. Ren, Z.; Zhang, C.; Ma, L.; Zhang, X.; Shi, S.; Tang, D.; Xu, J.; Hu, Y.; Wang, B.; Zhang, F.; et al. Lysophosphatidic acid induces the migration and invasion of SGC-7901 gastric cancer cells through the LPA2 and Notch signaling pathways. Int. J. Mol. Med. 2019, 44, 67–78.

28. Fukushima, K.; Otagaki, S.; Takahashi, K.; Minami, K.; Ishimoto, K.; Fukushima, N.; Honoki, K.; Tsujiuchi, T. Promotion of cell-invasive activity through the induction of LPA receptor-1 in pancreatic cancer cells. J. Recept. Signal Transduct. Res. 2018, 38, 367–371.

29. Fukushima, K.; Takahashi, K.; Yamasaki, E.; Onishi, Y.; Fukushima, N.; Honoki, K.; Tsujiuchi, T. Lysophosphatidic acid signaling via LPA1 and LPA3 regulates cellular functions during tumor progression in pancreatic cancer cells. Exp. Cell Res. 2017, 352, 139–145.

30. Obo, Y.; Yamada, T.; Furukawa, M.; Hotta, M.; Honoki, K.; Fukushima, N.; Tsujiuchi, T. Frequent mutations of lysophosphatidic acid receptor-1 gene in rat liver tumors. Mutat. Res. 2009, 660, 47–50.

31. Zhao, P.F.; Wu, S.; Li, Y.; Bao, G.; Pei, J.Y.; Wang, Y.W.; Ma, Q.; Sun, H.J.; Damirin, A. LPA receptor1 antagonists as anticancer agents suppress human lung tumours. Eur. J. Pharmacol. 2020, 868, 172886.

32. Amaral, R.F.; Geraldo, L.H.M.; Einicker-Lamas, M.E.; Spohr, T.C.L.S.; Mendes, F.; Lima, F.R.S. Microglial lysophosphatidic acid promotes glioblastoma proliferation and migration via LPA1 receptor. J. Neurochem. 2021, 156, 499–512.

33. Loskutov, Y.V.; Griffin, C.L.; Marinak, K.M.; Bobko, A.; Margaryan, N.V.; Geldenhuys, W.J.; Sarkaria, J.N.; Pugacheva, E.N. LPA signaling is regulated through the primary cilium: A novel target in glioblastoma. Oncogene 2018, 37, 1457–1471.

34. Valdés-Rives, S.A.; Arcos-Montoya, D.; de la Fuente-Granada, M.; Zamora-Sánchez, C.J.; Arias-Romero, L.E.; Villamar-Cruz, O.; Camacho-Arroyo, I.; Pérez-Tapia, S.M.; González-Arenas, A. LPA1 receptor promotes progesterone receptor phosphorylation through PKCα in human glioblastoma cells. Cells 2021, 10, 807.

35. Okabe, K.; Hayashi, M.; Fujii, M.; Honoki, K.; Mori, T.; Fukushima, N.; Tsujiuchi, T. Mutations of lysophosphatidic acid receptor genes in human osteosarcoma cells. Pathobiology 2010, 77, 278–282.

36. Cui, R.; Cao, G.; Bai, H.; Zhang, Z. LPAR1 regulates the development of intratumoral heterogeneity in ovarian serous cystadenocarcinoma by activating the PI3K/AKT signaling pathway. Cancer Cell Int. 2019, 19, 201.

37. Seo, E.J.; Kwon, Y.W.; Jang, I.H.; Kim, D.K.; Lee, S.I.; Choi, E.J.; Kim, K.H.; Suh, D.S.; Lee, J.H.; Choi, K.U.; et al. Autotaxin regulates maintenance of ovarian cancer stem cells through lysophosphatidic acid-mediated autocrine mechanis

m. Stem Cells 2016, 34, 551–564.

38. Li, T.T.; Alemayehu, M.; Aziziyeh, A.I.; Pape, C.; Pampillo, M.; Postovit, L.M.; Mills, G.B.; Babwah, A.V.; Bhattacharya, M. Beta-arrestin/Ral signaling regulates lysophosphatidic acid-mediated migration and invasion of human breast tumor cells. Mol. Cancer Res. 2009, 7, 1064–1077.

39. David, M.; Sahay, D.; Mege, F.; Descotes, F.; Leblanc, R.; Ribeiro, J.; Clézardin, P.; Peyruchaud, O. Identification of he parin-binding EGF-like growth factor (HB-EGF) as a biomarker for lysophosphatidic acid receptor type 1 (LPA1) activati on in human breast and prostate cancers. PLoS ONE 2014, 9, e97771.

40. Huang, Y.L.; Lin, Y.C.; Lin, C.C.; Chen, W.M.; Chen, B.P.C.; Lee, H. High glucose induces VEGF-C expression via the L PA1/3-Akt-ROS-LEDGF signaling axis in human prostate cancer pc-3 cells. Cell. Physiol. Biochem. 2018, 50, 597–611.

41. Lin, Y.C.; Chen, C.C.; Chen, W.M.; Lu, K.Y.; Shen, T.L.; Jou, Y.C.; Shen, C.H.; Ohbayashi, N.; Kanaho, Y.; Huang, Y.L.; et al. LPA1/3 signaling mediates tumor lymphangiogenesis through promoting CRT expression in prostate cancer. Bioc him. Biophys. Acta Mol. Cell Biol. Lipids 2018, 1863, 1305–1315.

42. Yu, S.; Murph, M.M.; Lu, Y.; Liu, S.; Hall, H.S.; Liu, J.; Stephens, C.; Fang, X.; Mills, G.B. Lysophosphatidic acid recepto rs determine tumorigenicity and aggressiveness of ovarian cancer cells. J. Natl. Cancer Inst. 2008, 100, 1630–1642.

43. Fujita, T.; Miyamoto, S.; Onoyama, I.; Sonoda, K.; Mekada, E.; Nakano, H. Expression of lysophosphatidic acid recepto rs and vascular endothelial growth factor mediating lysophosphatidic acid in the development of human ovarian cancer. Cancer Lett. 2003, 192, 161–169.

44. Huang, M.C.; Lee, H.Y.; Yeh, C.C.; Kong, Y.; Zaloudek, C.J.; Goetzl, E.J. Induction of protein growth factor systems in t he ovaries of transgenic mice overexpressing human type 2 lysophosphatidic acid G protein-coupled receptor (LPA2). Oncogene 2004, 23, 122–129.

45. Fang, X.; Yu, S.; Bast, R.C.; Liu, S.; Xu, H.J.; Hu, S.X.; LaPushin, R.; Claret, F.X.; Aggarwal, B.B.; Lu, Y.; et al. Mechani sms for lysophosphatidic acid-induced cytokine production in ovarian cancer cells. J. Biol. Chem. 2004, 279, 9653–966 1.

46. Pustilnik, T.B.; Estrella, V.; Wiener, J.R.; Mao, M.; Eder, A.; Watt, M.A.; Bast, R.C., Jr.; Mills, G.B. Lysophosphatidic acid induces urokinase secretion by ovarian cancer cells. Clin. Cancer Res. 1999, 5, 3704–3710.

47. Jeong, K.J.; Park, S.Y.; Seo, J.H.; Lee, K.B.; Choi, W.S.; Han, J.W.; Kang, J.K.; Park, C.G.; Kim, Y.K.; Lee, H.Y. Lysoph osphatidic acid receptor 2 and Gi/Src pathway mediate cell motility through cyclooxygenase 2 expression in CAOV-3 ov arian cancer cells. Exp. Mol. Med. 2008, 40, 607–616.

48. Park, J.; Jang, J.H.; Oh, S.; Kim, M.; Shin, C.; Jeong, M.; Heo, K.; Park, J.B.; Kim, S.R.; Oh, Y.S. LPA-induced migratio n of ovarian cancer cells requires activation of ERM proteins via LPA1 and LPA2. Cell Signal. 2018, 44, 138–147.

49. Yun, C.C.; Sun, H.; Wang, D.; Rusovici, R.; Castleberry, A.; Hall, R.A.; Shim, H. LPA2 receptor mediates mitogenic sign als in human colon cancer cells. Am. J. Physiol. Cell Physiol. 2005, 289, C2–C11.

50. Li, M.; Xiao, D.; Zhang, J.; Qu, H.; Yang, Y.; Yan, Y.; Liu, X.; Wang, J.; Liu, L.; Wang, J.; et al. Expression of LPA2 is ass ociated with poor prognosis in human breast cancer and regulates HIF-1α expression and breast cancer cell growth. O ncol. Rep. 2016, 36, 3479–3487.

51. Lin, S.; Wang, D.; Iyer, S.; Ghaleb, A.M.; Shim, H.; Yang, V.W.; Chun, J.; Yun, C.C. The absence of LPA2 attenuates tu mor formation in an experimental model of colitis-associated cancer. Gastroenterology 2009, 136, 1711–1720.

52. Komachi, M.; Tomura, H.; Malchinkhuu, E.; Tobo, M.; Mogi, C.; Yamada, T.; Kimura, T.; Kuwabara, A.; Ohta, H.; Im, D. S.; et al. LPA1 receptors mediate stimulation, whereas LPA2 receptors mediate inhibition, of migration of pancreatic ca ncer cells in response to lysophosphatidic acid and malignant ascites. Carcinogenesis 2009, 30, 457–465.

53. Lin, F.T.; Lai, Y.J.; Makarova, N.; Tigyi, G.; Lin, W.C. The lysophosphatidic acid 2 receptor mediates down-regulation of Siva-1 to promote cell survival. J. Biol. Chem. 2007, 282, 37759–37769.

54. Shuyu, E.; Lai, Y.J.; Tsukahara, R.; Chen, C.S.; Fujiwara, Y.; Yue, J.; Yu, J.H.; Guo, H.; Kihara, A.; Tigyi, G.; et al. Lysop hosphatidic acid 2 receptor-mediated supramolecular complex formation regulates its antiapoptotic effect. J. Biol. Che m. 2009, 284, 14558–14571.

55. Deng, W.; Wang, D.A.; Gosmanova, E.; Johnson, L.R.; Tigyi, G. LPA protects intestinal epithelial cells from apoptosis b y inhibiting the mitochondrial pathway. Am. J. Physiol. Gastrointest. Liver Physiol. 2003, 284, G821–G829.

56. Zuckerman, V.; Sokolov, E.; Swet, J.H.; Ahrens, W.A.; Showlater, V.; Iannitti, D.A.; Mckillop, I.H. Expression and functio n of lysophosphatidic acid receptors (LPARs) 1 and 3 in human hepatic cancer progenitor cells. Oncotarget 2016, 7, 29 51–2967.

57. Altman, M.K.; Gopal, V.; Jia, W.; Yu, S.; Hall, H.; Mills, G.B.; McGinnis, A.C.; Bartlett, M.G.; Jiang, G.; Madan, D.; et al. Targeting melanoma growth and viability reveals dualistic functionality of the phosphonothionate analogue of carba cycl

ic phosphatidic acid. Mol. Cancer 2010, 9, 140.

58. Jia, W.; Tran, S.K.; Ruddick, C.A.; Murph, M.M. The Src homology 3 binding domain is required for lysophosphatidic aci d 3 receptor-mediated cellular viability in melanoma cells. Cancer Lett. 2015, 356, 589–596.

59. Cai, H.; Xu, Y. The role of LPA and YAP signaling in long-term migration of human ovarian cancer cells. Cell Commun. Signal. 2013, 11, 31.

60. Burkhalter, R.J.; Westfall, S.D.; Liu, Y.; Stack, M.S. Lysophosphatidic acid initiates epithelial to mesenchymal transition and induces β-Catenin-mediated transcription in epithelial ovarian carcinoma. J. Biol. Chem. 2015, 290, 22143–22154.

61. Kato, K.; Yoshikawa, K.; Tanabe, E.; Kitayoshi, M.; Fukui, R.; Fukushima, N.; Tsujiuchi, T. Opposite roles of LPA1 and L PA3 on cell motile and invasive activities of pancreatic cancer cells. Tumour. Biol. 2012, 33, 1739–1744.

62. Sun, K.; Cai, H.; Duan, X.; Yang, Y.; Li, M.; Qu, J.; Zhang, X.; Wang, J. Aberrant expression and potential therapeutic ta rget of lysophosphatidic acid receptor 3 in triple-negative breast cancers. Clin. Exp. Med. 2015, 15, 371–380.

63. Tanabe, E.; Kitayoshi, M.; Yoshikawa, K.; Shibata, A.; Honoki, K.; Fukushima, N.; Tsujiuchi, T. Loss of lysophosphatidic acid receptor-3 suppresses cell migration activity of human sarcoma cells. J. Recept. Signal Transduct. Res. 2012, 32, 328–334.

64. Li, G.C.; Qin, X.L.; Song, H.H.; Li, Y.N.; Qiu, Y.Y.; Cui, S.C.; Wang, Y.S.; Wang, H.; Gong, J.L. Upregulated microRNA-1 5b alleviates ovarian cancer through inhitbition of the PI3K/Akt pathway by targeting LPAR3. J. Cell. Physiol. 2019, 23 4, 22331–22342.

65. Ishii, S.; Hirane, M.; Fukushima, K.; Tomimatsu, A.; Fukushima, N.; Tsujiuchi, T. Diverse effects of LPA4, LPA5 and LPA 6 on the activation of tumor progression in pancreatic cancer cells. Biochem. Biophys. Res. Commun. 2015, 461, 59–6 4.

66. Lee, Z.; Cheng, C.T.; Zhang, H.; Subler, M.A.; Wu, J.; Mukherjee, A.; Windle, J.J.; Chen, C.K.; Fang, X. Role of LPA4/p 2y9/GPR23 in negative regulation of cell motility. Mol. Biol. Cell 2008, 19, 5435–5445.

67. Takahashi, K.; Fukushima, K.; Onishi, Y.; Inui, K.; Node, Y.; Fukushima, N.; Honoki, K.; Tsujiuchi, T. Lysophosphatidic a cid (LPA) signaling via LPA4 and LPA6 negatively regulates cell motile activities of colon cancer cells. Biochem. Biophy s. Res. Commun. 2017, 483, 652–657.

68. Matayoshi, S.; Chiba, S.; Lin, Y.; Arakaki, K.; Matsumoto, H.; Nakanishi, T.; Suzuki, M.; Kato, S. Lysophosphatidic acid r eceptor 4 signaling potentially modulates malignant behavior in human head and neck squamous cell carcinoma cells. I nt. J. Oncol. 2013, 42, 1560–1568.

69. Eino, D.; Tsukada, Y.; Naito, H.; Kanemura, Y.; Iba, T.; Wakabayashi, T.; Muramatsu, F.; Kidoya, H.; Arita, H.; Kagawa, N.; et al. LPA4-mediated vascular network formation increases the efficacy of anti-PD-1 therapy against brain tumors. Cancer Res. 2018, 78, 6607–6620.

70. Harper, K.; Arsenault, D.; Boulay-Jean, S.; Lauzier, A.; Lucien, F.; Dubois, C.M. Autotaxin promotes cancer invasion via the lysophosphatidic acid receptor 4: Participation of the cyclic AMP/EPAC/Rac1 signaling pathway in invadopodia form ation. Cancer Res. 2010, 70, 4634–4643.

71. Yasuda, D.; Kobayashi, D.; Akahoshi, N.; Ohto-Nakanishi, T.; Yoshioka, K.; Takuwa, Y.; Mizuno, S.; Takahashi, S.; Ishii, S. Lysophosphatidic acid-induced YAP/TAZ activation promotes developmental angiogenesis by repressing Notch ligan d Dll4. J. Clin. Investig. 2019, 129, 4332–4349.

72. Dong, L.; Lin, F.; Wu, W.; Huang, W.; Cai, Z. Transcriptional cofactor Mask2 is required for YAP-induced cell growth and migration in bladder cancer cell. J. Cancer 2016, 7, 2132–2138.

73. He, L.; Wu, M.Z.; Wang, X.B.; Qiu, X.S.; Wang, E.H.; Wu, G.P. Tumor Suppressor LKB1 inhibits both the mRNA expres sion and the amplification of hTERC by the phosphorylation of YAP in lung cancer cells. J. Cancer 2019, 10, 3632–363 8.

74. Araki, M.; Kitayoshi, M.; Dong, Y.; Hirane, M.; Ozaki, S.; Mori, S.; Fukushima, N.; Honoki, K.; Tsujiuchi, T. Inhibitory effe cts of lysophosphatidic acid receptor-5 on cellular functions of sarcoma cells. Growth Factors 2014, 32, 117–122.

75. Okabe, K.; Hayashi, M.; Yamawaki, Y.; Teranishi, M.; Honoki, K.; Mori, T.; Fukushima, N.; Tsujiuchi, T. Possible involve ment of lysophosphatidic acid receptor-5 gene in the acquisition of growth advantage of rat tumor cells. Mol. Carcinog. 2011, 50, 635–642.

76. Zhao, W.J.; Zhu, L.L.; Yang, W.Q.; Xu, S.J.; Chen, J.; Ding, X.F.; Liang, Y.; Chen, G. LPAR5 promotes thyroid carcinom a cell proliferation and migration by activating class IA PI3K catalytic subunit p110β. Cancer Sci. 2021, 112, 1624–163 2.

77. Lee, S.C.; Fujiwara, Y.; Liu, J.; Yue, J.; Shimizu, Y.; Norman, D.D.; Wang, Y.; Tsukahara, R.; Szabo, E.; Patil, R.; et al. A utotaxin and LPA1 and LPA5 receptors exert disparate functions in tumor cells versus the host tissue microenvironment

in melanoma invasion and metastasis. Mol. Cancer Res. 2015, 13, 174–185.

78. Jongsma, M.; Matas-Rico, E.; Rzadkowski, A.; Jalink, K.; Moolenaar, W.H. LPA is a chemorepellent for B16 melanoma cells: Action through the cAMP-elevating LPA5 receptor. PLoS ONE 2011, 6, e29260.
79. Mathew, D.; Kremer, K.N.; Strauch, P.; Tigyi, G.; Pelanda, R.; Torres, R.M. LPA5 is an inhibitory receptor that suppresse s CD8 T-cell cytotoxic function via disruption of early TCR signaling. Front. Immunol. 2019, 10, 1159.
80. Mazzocca, A.; Dituri, F.; De Santis, F.; Filannino, A.; Lopane, C.; Betz, R.C.; Li, Y.Y.; Mukaida, N.; Winter, P.; Tortorella, C.; et al. Lysophosphatidic acid receptor LPAR6 supports the tumorigenicity of hepatocellular carcinoma. Cancer Res. 2015, 75, 532–543.
81. Enooku, K.; Uranbileg, B.; Ikeda, H.; Kurano, M.; Sato, M.; Kudo, H.; Maki, H.; Koike, K.; Hasegawa, K.; Kokudo, N.; et al. Higher LPA2 and LPA6 mRNA Levels in hepatocellular carcinoma are associated with poorer differentiation, microva scular invasion and earlier recurrence with higher serum autotaxin levels. PLoS ONE 2016, 11, e0161825.
82. Zheng, X.; Jia, Y.; Qiu, L.; Zeng, X.; Xu, L.; Wei, M.; Huang, C.; Liu, C.; Chen, L.; Han, J. A potential target for liver canc er management, lysophosphatidic acid receptor 6 (LPAR6), is transcriptionally up-regulated by the NCOA3 coactivator. J. Biol. Chem. 2020, 295, 1474–1488.
83. Takahashi, K.; Fukushima, K.; Otagaki, S.; Ishimoto, K.; Minami, K.; Fukushima, N.; Honoki, K.; Tsujiuchi, T. Effects of L PA1 and LPA6 on the regulation of colony formation activity in colon cancer cells treated with anticancer drugs. J. Rece pt. Signal Transduct. Res. 2018, 38, 71–75.