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MINI REVIEW

Roles of lysophosphatidic acid (LPA) receptor-mediated signaling in cancer cell biology

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Abstract

Lysophosphatidic acid (LPA) is a simple lipid which is endogenously synthesized from lysophosphatidylcholine (LPC) by autotaxin (ATX). LPA mediates a variety of cellular responses through the binding of G protein-coupled LPA receptors (LPA_1 to LPA_6). It is considered that LPA receptor-mediated signaling plays an important role in the pathogenesis of human malignancy. Genetic alterations and epigenetic changes of LPA receptors have been detected in some cancer cells as well as LPA per se. Moreover, LPA receptors contribute to the promotion of tumor progression, including cell proliferation, invasion, metastasis, tumorigenicity, and angiogenesis. In recent studies, the activation of LPA receptor-mediated signaling regulates chemoresistance and radiosensitivity in cancer cells. This review provides an updated overview on the roles of LPA receptor-mediated signaling in the regulation of cancer cell functions and its potential utility as a molecular target for novel therapies in clinical cancer approaches.

Keywords LPA · LPA receptors · Cancer cell functions · Tumor progression · Cancer cells

Introduction

Lysophosphatidic acid (LPA) is an extracellular lipid which evokes the intracellular signaling via binding to G-protein-coupled LPA receptors. At least six subtypes of LPA receptors (LPA receptor-1 (LPA_1) to LPA_6) have been determined. LPA signaling via LPA receptors indicates a variety of cellular responses, including cell growth, differentiation, morphogenesis, cell migration and protection from apoptosis (Geraldo et al. 2021; Stoddard and Chun 2015; Aikawa et al. 2015; Yung et al. 2014). The biological functions of the individual LPA receptors are not uniform, dependent on types of cells. It is considered that LPA receptor-mediated signaling plays an important role in the pathogenesis of human disease, such as cardiovascular disease, neuropathic pain, fibrosis and cancer (Lin et al. 2010; Tsujiuchi et al. 2014).

In the 1990s, Xu et al. reported that LPA was highly secreted in serum and ascites in aggressive ovarian cancers (Xu et al. 1995). Subsequently, numerous studies have indicated the involvement of LPA receptors in cancer cell biology as well as LPA per se. Genetic alterations and epigenetic changes of LPA receptor genes occur in some cancer cells. Moreover, LPA receptors participate in the promotion of tumor progression, such as cell proliferation, invasion, metastasis, tumorigenicity and angiogenesis (Lin et al. 2010; Tsujiuchi et al. 2014). In recent studies, the activation of LPA receptor-mediated signaling modulates chemoresistance and radiosensitivity in cancer cells (Ueda et al. 2020; Minami et al. 2019; Okuda et al. 2023). Therefore, it is suggested that LPA receptor-mediated signaling may be a target molecule for novel therapies in clinical cancer approaches. In this review, we provide an updated overview on the current evidence of the roles of LPA receptor-mediated signaling in the regulation of cancer cell functions.

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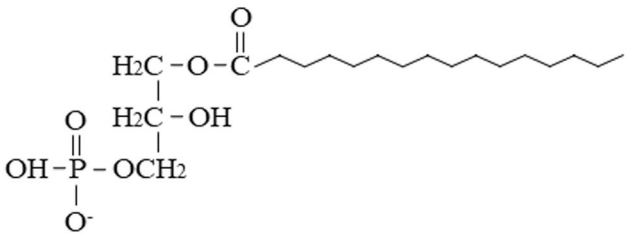

Fig. 1 Structure of 16:0-LPA. 16:0-LPA is one of the most abundant forms in human plasma (Sano et al. 2002)

LPA

LPA is a simple lipid and structurally consists of a glycerol, a fatty acid and a phosphate (Geraldo et al. 2021; Stoddard and Chun 2015; Aikawa et al. 2015). In 1970s, LPA is identified as a physiological molecule which modulates platelet aggregation, intracellular calcium release and blood pressure (Tokumura et al. 1978; Gerrard et al. 1979). LPA is found in not only all mammalian cells and tissues, but also in plasma, serum and saliva (Geraldo et al. 2021; Stoddard and Chun 2015; Aikawa et al. 2015). LPA is released from activated platelets and detectable at concentrations of approximately 1 to 5 μM in serum (Eichholtz et al. 1993). LPA is present as a mixture of several fatty acids in vivo condition; unsaturated fatty acids (16:1, 18:1, 18:2 and 20:4) and saturated fatty acids (16:0, 18:0) (Aoki et al. 2008). In human plasma, the most abundant LPA forms are 16:0, 18:2 and 18:1 (Sano et al. 2002) (Fig. 1). It is considered that there are at least two pathways for LPA synthesis. LPA is endogenously synthesized from lysophosphatidylcholine (LPC) by autotaxin (ATX). ATX is widely present in biological fluids, such as plasma, cerebrospinal fluid, synovial fluid and cancer ascites (Stracke et al. 1992). Conversely, membrane-bound phosphatidic acid-preferring phospholipase A1 also catalyzes the conversion of phosphatidic acid (PA) to LPA (Aoki et al. 2008).

LPA receptors

LPA receptors are members of G protein-coupled receptors (GPCR) (Arang and Gutking 2020). So far, six subtypes of LPA receptors have been identified as LPA_1/EDG2, LPA_2/EDG4, LPA_3/EDG7, LPA_4/P2Y9/GPR23, LPA_5/GPR92 and LPA_6/P2Y5 (Choi et al. 2008; Ishii et al. 2009). Additionally, LPA receptors are classified into two groups. LPA_1, LPA_2 and LPA_3 belong to the endothelial cell differentiation gene (Edg) family. Conversely, LPA_4, LPA_5 and LPA_6 have been determined as non-Edg LPA receptors which are the purinergic receptor family. These receptors are structurally distance from other LPA receptors (Choi et al. 2008; Ishii et al. 2009). LPA receptors are coupled to individual sets of G proteins (Gi, Gq, Gs and G12/13) and mediate a large variety of LPA effector functions (Table 1). The effects of each LPA receptor on cellular responses are not equivalent. For instance, LPA_1 and LPA_2 stimulate cell proliferation, intracellular calcium mobilization, adenylyl cyclase inhibition and phospholipase C activation (Geraldo et al. 2021). LPA_3 increases axon branching via the activation of Gq protein in neural cells (Furuta et al. 2012). LPA_4 and LPA_5 provoke neurite retraction and stress fiber formation of neural cells (Geraldo et al. 2021). LPA_6 is involved in the maintenance of human hair growth. In addition, homozygous mutation of LPA_6 gene is the cause of hypotrichosis (Pasternack et al. 2008; Shimomura et al. 2009).

Table 1 LPA receptors

Receptor	G proteins
LPA_1	$G_{12/13}$, Gq, Gi
LPA_2	$G_{12/13}$, Gq, Gi
LPA_3	Gq, Gi
LPA_4	$G_{12/13}$, Gq, Gi, Gs
LPA_5	$G_{12/13}$, Gq
LPA_6	$G_{12/13}$, Gq, Gi, Gs

Roles of LPA signaling via LPA receptors in the pathogenesis of cancer cells

It has been reported that genetic and epigenetic alterations of LPA receptors are detected in cancer cells as well as LPA per se (Tsujiuchi et al. 2014). LPA is present at high concentrations in blood and ascites from ovarian cancer patients (Xu et al. 1995). In colon and gastric cancer cells, LPA contributes to the modulation of cell proliferation, migration and adhesion (Shida et al. 2003, 2004a). Moreover, ATX overexpression is associated with the promotion of malignant potency during tumor progression in several cancer cells (Samadi et al. 2011; Leblanc and Peyruchaud 2015; van Meeteren and Moolenaar 2007). Mutations of *LPAR2* and *LPAR4* genes are found in colon cancer cells (Tsujino et al. 2010). *LPAR1* and *LPAR3* mutations occur in osteosarcoma, while no mutation of LPA receptors is detected in in fibrosarcoma cells (Okabe et al. 2010). In contrast, rodent tumors induced by chemical carcinogens harbor high frequent mutations of *Lpar1* gene. *Lpar1* gene mutations are detected 46.7% in rat liver tumors induced by N-nitrosodiethylamine (Obo et al. 2009). Moreover, the frequency of *Lpar1* gene mutations is 16.7% in adenomas and 41.2% in adenocarcinomas during rat lung carcinogenesis induced by N-nitrosobis(2-hydroxypropyl)amine (Yamada et al. 2009). Mutant LPA_1 positively regulates malignant properties of cancer cells (Hayashi et al. 2012; Kato et al. 2012). Aberrant LPA receptor expressions

are detected in human cancer cells. LPA_2 expressions are significantly higher in thyroid and breast cancer cells than in normal tissues, but not LPA_1 expressions (Schulte et al. 2001). The expression levels of LPA_2 are increased in breast cancer cells, while no change of LPA_1 and LPA_3 expressions is observed (Kitayama et al. 2004). LPA_1 expressions are elevated and LPA_2 expressions are reduced in colorectal cancers, compared with normal surrounding tissues (Shida et al. 2004b). In addition, loss of LPA receptor expressions is due to hyper DNA methylation of the promoter region of LPA receptor genes in colon cancer and osteosarcoma cells (Tsujino et al. 2010; Okabe et al. 2011).

Regulation of cellular functions via LPA receptor-mediated signaling in cancer cells

Pancreatic cancer cells

The cell motile and invasive activities of pancreatic cancer cells are stimulated by LPA1, LPA_3 and LPA_6. Conversely, LPA_2, LPA_4 and LPA_5 inhibit the cell motility and invasion of pancreatic cancer cells. The activation of matrix metalloproteinase-2 (MMP-2) is elevated by LPA_1, LPA_2, LPA_5 and LPA_6 (Fukushima et al. 2017; Komachi et al. 2009; Ishii et al. 2015). In addition, the cell motility is decreased by culturing in low glucose mediums, while *LPAR1* and *LPAR2* expression levels are increased (Takai et al. 2023). It is well known that MMP-2 activation participates in the promotion of cancer cell invasion and metastasis during tumor progression as well as MMP-9 (Kessenbrock et al. 2010). In colony assay, LPA_1, LPA_3 and LPA_6 enhance the colony formation of pancreatic cancer cells, while LPA_4 and LPA_5 inhibit (Fukushima et al. 2017; Ishii et al. 2015). ATX-LPA axis promotes tumor progression of pancreatic cancer cells, such as peritoneal seeding and malignant ascites (Jinno et al. 2021).

Gastrointestinal cancer cells

In gastric cancer cells, the cell migration of *LPAR1*-expressing cells is increased by LPA, but not *LPAR2*-expressing cells (Shida et al. 2004a). In colon cancer cells, LPA stimulated the cell proliferation, migration and adhesion of *LPAR1*-expressing cells. In contrast, LPA did not affect the cell migration and adhesion of *LPAR*2-expressing cells, whereas it increased the cell growth activity (Shida et al. 2003). LPA facilitates the colon cancer cell growth activity through ROCK and STAT-3 pathways (Leve et al. 2018). The cell motility and invasion of colon cancer cells are suppressed by LPA_3, LPA_4 and LPA_6 (Fukui et al. 2012; Takahashi et al. 2017a). While LPA_1 forms the large sized colonies of colon cancer cells, the colony formation is decreased by LPA_6 (Takahashi et al. 2018a). LPA induces the secretion of angiogenic factors through LPA_1 and LPA_2 in colon cancer cells (Shida et al. 2003).

Ovarian cancer cells

The cell death is promoted through apoptosis and anoikis by LPA in highly LPA_1-expressing cells, while LPA inhibits the cell growth activity (Furui et al. 1999; Fang et al. 2002). The expression levels of vascular endothelial growth factor (VEGF) are associated with LPA_2 and LPA_3 expression levels in ovarian cancer cells (Fujita et al. 2003). LPA_2 knockdown inhibits the production of VEGF as well as LPA_3 knockdown (Yu et al. 2008). LPA increases VEGF mRNA expression and protein secretion (Hu et al. 2001). The cell motility and invasion of ovarian cancer cells are elevated by LPA_3. In mouse xenograft study, LPA_2 and LPA_3 enhance tumor growth, ascites formation and metastatic potency to distant organs, resulting in the reduction of the survival rate of mice (Yu et al. 2008).

Bone and soft tissue sarcoma cells

The cell motility and invasion of fibrosarcoma cells are stimulated by LPA_2 (Takahashi et al. 2017b). In highly migratory osteosarcoma cells, the cell motile activity is closely associated with *LPAR2* gene expression (Takahashi et al. 2018b). The cell motile activity of osteosarcoma cells is stimulated via LPA_2-mediated signaling activated by culturing with endothelial cells (Minami et al. 2021). In soft-agar colony formation assay, LPA_2 enhances the colony formation activity in fibrosarcoma and osteosarcoma cells (Takahashi et al. 2017b, 2018b). In contrast, LPA_1-mediated signaling suppresses pulmonary metastasis of osteosarcoma cells (Takagi et al. 2021). The cell motile and invasive activities are reduced by LPA_5 in osteosarcoma and fibrosarcoma cells (Minami et al. 2020a; Dong et al. 2014).

Others

In neuroblastoma cells, the cell motility and invasion are elevated by LPA_2 and LPA_3. Although wild-type LPA_1 suppresses the cell motility and MMP-2 activation, mutant LPA_1 has promoting effects. Moreover, mutant LPA_1 enhances the colony formation as well as LPA_3 (Hayashi et al. 2012; Kato et al. 2012). In lung cancer cells, the cell motile activity is suppressed by LPA_1 and LPA_2. Conversely, LPA_3 stimulates the cell motile activity and inhibited angiogenesis (Ueda et al. 2020; Tanabe et al. 2013). The cell motility and invasion of hepatoma cells are stimulated by LPA_3. LPA_3 enhances the colony formation of hepatoma cells (Okabe et al. 2013).

Chemoresistance via activation of LPA receptor-mediated signaling

Multidrug resistance is a pharmacological phenomenon of the simultaneous tolerance to functionally and structurally unrelated anticancer drugs and toxic compounds. The acquisition of multidrug resistance is one of the major causes of chemotherapeutic failure during cancer treatment (Hamilton and Rath 2014). It has been reported that LPA receptor-mediated signaling participates in the modulation of chemoresistance of cancer cells. In ovarian cancer cells, LPA_1-expressing cells shows the low cell proliferation activity and high cell viability to CDDP, compared with LPA_1-unexpressing cells (Furui et al. 1999). The cell survival rate to CDDP is enhanced through LPA_2-mediated signaling in fibrosarcoma, osteosarcoma and lung cancer cells (Ueda et al. 2020; Minami et al. 2020b; Kurisu et al. 2022). The cell survival is elevated by LPA_3 in hepatoma cells treated with CDDP and doxorubicin (Okabe et al. 2013). In contrast, LPA_3 decreases the cell survival rate to CDDP of lung cancer and osteosarcoma cells (Ueda et al. 2020; Kurisu et al. 2022). LPA_5 reduces the cell survival to CDDP of osteosarcoma cells (Minami et al. 2020a). The cell survival is decreased by LPA_5 in melanoma cells treated with CDDP and dacarbazine (Minami et al. 2019). The cell survival to CDDP is suppressed through apoptosis by LPA_4 and LPA_6 in osteosarcoma cells (Kurisu et al. 202).

It is considered that activation of ATP-binding cassette (ABC) transporters and drug-detoxifying enzyme facilitates the acquisition of multidrug resistance in cancer cells. ABC transporters act as the efflux pumps of anticancer drugs through the cell membrane. ABC transporters are composed of at least 48 members. In particular, ABCB1, ABCC1, ABCC10 and ABCG2 contribute to the promotion of multidrug resistance. ABC transporters requires abundant ATP production as the energy molecule in cancer cells (Kathawala et al. 2015; Chen et al. 2016; Sau et al. 2010). It is suggested that the depletion of intracellular ATP may result in the suppression of chemoresistance through ABC transporters. In the presence of LPA, the cell survival to CDDP is decreased in ATP-reduced osteosarcoma cells (Kurisu et al. 2022). On the other hand, ATP is used as the substrate for cAMP synthesis by adenylyl cyclase activity (Steegborn 2014). cAMP induces apoptosis and promotes chemoresistance in some types of tumor cells (Zhang et al. 2020; Insel et al. 2012). Gs protein stimulates and Gi protein suppresses the adenylyl cyclase activity (Stoddard and Chun 2015). Therefore, the differential effects of the individual LPA receptors on cell survival to anticancer drugs may be due to the intracellular cAMP accumulation levels in cancer cells. Moreover, Rho family is involved in the regulation of chemosensitivity to CDDP (Mokady et al. 2015). G12/13 protein activates Rho signaling pathway (Geraldo et al. 2021). While RhoA and RhoC have the antiapoptotic effects, resulting in chemoresistance to CDDP, the proapoptosis induced by RhoB activation enhances chemosensitivity to CDDP (Mokady et al. 2015). In the presence of LPA_2 agonist, the cell survival to CDDP of fibrosarcoma cells is inhibited by RhoA and RhoC knockdowns (Minami et al. 2020b) (Fig. 2).

Involvement of LPA receptor-mediated signaling in radiation sensitivity

Radiation is one of the common treatments for a variety of cancers as well as chemotherapy. Ionizing radiation directly produces DNA damage and induces DNA double-strand breaks, resulting in tumor cell death (Huang and Zhou 2020). The activation of LPA_2 promotes the response to DNA damage induced by gamma irradiation. Exposure to gamma irradiation elevates the expression level of *LPAR2* gene in intestinal epithelial cells. In mouse models, treatment of gamma irradiation increases the plasma ATX activity and LPA concentrations (Balogh et al. 2015). Furthermore, *LPAR2* gene expressions are increased in fibrosarcoma, pancreatic and lung cancer cells irradiated with X-rays. The cell motile activity of pancreatic cancer cells is reduced through LPA_2 by X-ray irradiation. On the other hand, the cell survival to X-ray irradiation is enhanced by the activation of LPA_2-mediated signaling in pancreatic cancer cells (Okuda et al. 2023).

Cancer stem cell and LPA receptor-mediated signaling

Cancer stem cells (CSCs) are conceptually proposed as a subpopulation of tumor cells exhibiting stem cell properties like self-renewal, sphere-forming and multi-lineage differentiation ability. CSCs are considered to be tumor initiating cells and could be an origin for tumor heterogeneity and involved in metastasis and relapse (Visvader and Lindeman 2008). CSCs has been identified in various types of hematologic and solid cancers (Bonnet and Dick 1997; Hermann et al. 2007; Al-Hajj et al. 2003; Fujii et al. 2009; Honoki et al. 2010). Various mechanisms are implicated in the evasion of CSC from therapy such as enhanced DNA damage repair, altered cell cycle checkpoint control and overexpression of multidrug resistance proteins (Morrison et al. 2011).

In ovarian cancer cells, LPA treatment stimulates the expression of CSC-associated stem cell marker genes, including OCT4, SOX2, ALDH1 and drug transporters. Moreover, LPA promotes CSC-like characteristics:

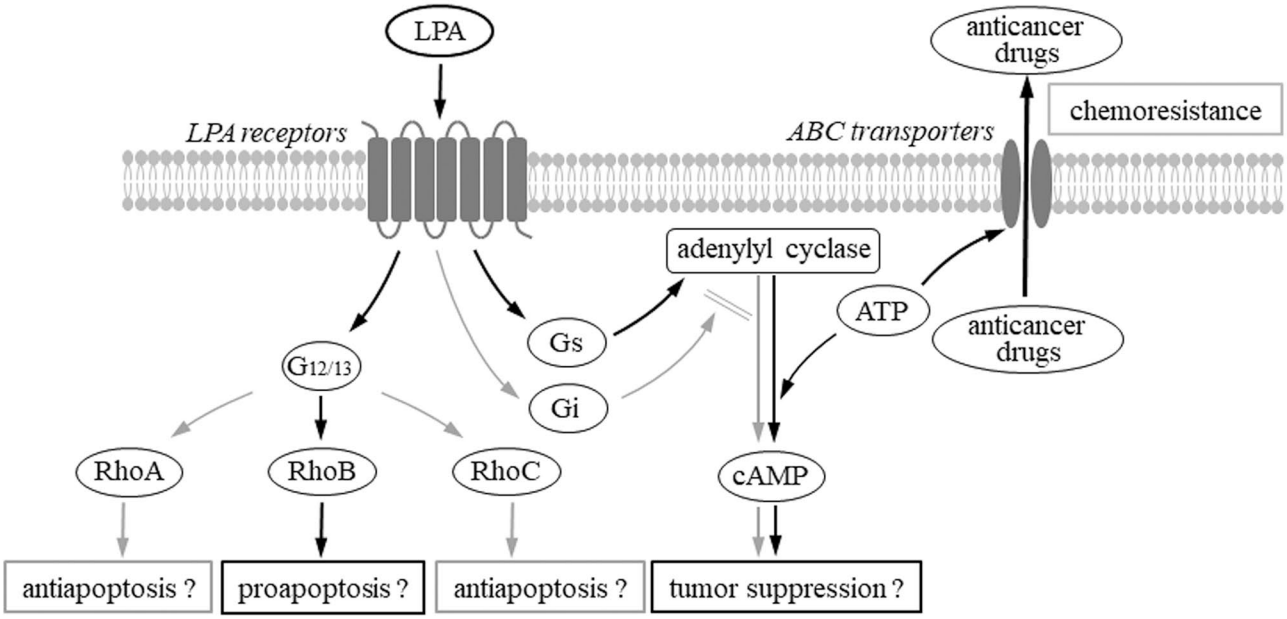

Fig. 2 Roles of LPA signaling via LPA receptors in the regulation of cell survival to anticancer drugs in cancer cells. Gi protein inhibits and Gs protein stimulates adenylyl cyclase activity. The increased amount of cAMP causes tumor suppression, such as apoptosis. ABC transporters require the abundant ATP to excrete chemotherapeutic agents across cellular membrane. G12/13 protein activates Rho-mediated signaling. RhoA and RhoC have the antiapoptotic effects, resulting in chemoresistance. RhoB induces the proapoptosis in cancer cells treated with anticancer drugs

epithelial-to-mesenchymal transition, sphere forming ability and resistance to anti-cancer drugs. Therefore, it is suggested that LPA plays a key role in the therapeutic resistance and tumor progression of ovarian CSCs (Seo et al. 2016).

ATX-LPA signaling axis participates in the interaction between tumor cells and tumor environment through the crosstalk of tumor cells and tumor-associated fibroblasts originated from mesenchymal stem cells (MSCs). Accumulating evidence suggests that MSCs promote in vivo growth of xenograft transplanted tumors as well as animal models (Huang et al. 2013; Tsukamoto et al. 2012). Interestingly, cancer-derived LPA facilitates the differentiation of human MSCs to myofibroblast-like cells (Jeon et al. 2008). Furthermore, LPA signaling promotes the secretion of cytokines like vascular endothelial growth factor and stromal cell-derived factor-1/CXCL12 from MSCs (Ptaszynska et al. 2010; Jeon et al. 2010). Taken together, targeting of ATX-LPA signaling pathway could be a potential therapeutic candidate to overcome the therapy-resistance and disease relapse as well as metastatic spreading in cancer.

Conclusion

In this review, we provide an overview of the pivotal roles of LPA receptor-mediated signaling in the regulation of cancer cell functions. LPA receptor-mediated signaling consists of complicated components of G protein-coupled LPA receptors and involved in several physiological functions of normal and cancer cells. Therefore, further efforts should be attempted to clarify the specific molecular mechanisms linked to LPA receptor-mediated signaling in cancer cells and establish a novel therapeutic approach for cancer treatment.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Compliance with ethical standards Not applicable.

Consent for publication Not applicable.

References

Aikawa S, Hashimoto T, Kano K, Aoki J (2015) Lysophosphatidic acid as a lipid mediator with multiple biological actions. J Biochem 157:81–89

Al-Hajj M, Wicha MS, Benito-Hernandez A, Morrison SJ, Clarke MF (2003) Prospective identification of tumorigenic breast cancer cells. Proc Natl Acad Sci USA 100:3983–3988

Aoki J, Inoue A, Okudaira S (2008) Two pathway for lysophosphatidic acid production. Biochim Biophys Acta 1781:513–518

Arang N, Gutking JS (2020) G protein-coupled receptors and heterotrimeric G proteins as cancer drivers. FEBS Lett 594:4201–4232

Balogh A, Shimizu Y, Lee SC, Norman DD, Gangwar R, Bavaria M, Moon C, Shukla P, Rao R, Ray R, Naren AP, Banerje S, Miller DD, Balazs L, Pelus L, Tigyi G (2015) The autotaxin-LPA_2 GPCR axis is modulated by γ-irradiation and facilitates DNA damage repair. Cell Signal 27:1751–1762

Bonnet D, Dick JE (1997) Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. Nat Med 3:730–737

Chen Z, Shi T, Zhang L, Zhu P, Deng M, Huang C, Hu T, Jiang L, Li J (2016) Mammalian drug efflux transporters of the ATP binding cassette (ABC) family in multidrug resistance: a review of the past decade. Cancer Lett 370:153–164

Choi JW, Lee CW, Chun J (2008) Biological roles of lysophospholipid receptors revealed by genetic null mice: an update. Biochim Biophys Act 1781:531–539

Dong Y, Hirane M, Araki M, Fukushima N, Honoki K, Tsujiuchi T (2014) Lysophosphatidic acid receptor-5 regulates cells motile and invasive avtivities of human sarcoma cell lines. Mol Cell Biochem 393:17–22

Eichholtz T, Jalink K, Fahrenfort I, Moolenaar WH (1993) The bioactive phospholipid lysophosphatidic acid is released from activated platelets. Biochem J 291:677–680

Fang X, Schummer M, Mao M, Yu S, Tabassam FH, Swaby R, Hasegawa Y, Tanyi JL, LaPushin R, Eder A, Jaffe R, Erickson J, Mills GB (2002) Lysophosphatidic acid is a bioactive mediator in ovarian cancer. Biochim Biophys Acta 1582:257–264

Fujii H, Honoki K, Tsujiuchi T, Kido A, Yoshitani K, Takakura Y (2009) Sphere-forming stem-like cell populations with drug resistance in human sarcoma cell lines. Int J Oncol 34:1381–1386

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

Fukui R, Tanabe E, Kitayoshi M, Yoshikawa K, Fukushima N, Tsujiuchi T (2012) Negative regulation of cell motile and invasive activities by lysophosphatidic acid receptor-3 in colon cancer HCT116 cells. Tumor Biol 33:1899–1905

Fukushima K, Takahashi K, Yamasaki E, Onishi Y, Fukushima N, Honoki K, Tsujiuchi T (2017) Lysophosphatidic acid signaling via LPA_1 and LPA_3 regulates cellular functions during tumor progression in pancreatic cancer cells. Exp Cell Res 352:139–145

Furui T, LaPushin R, Mao M, Khan H, Watt SR, Watt MAV, Lu Y, Fang X, Tsutsui S, Siddik ZH, Bast RC Jr, Mills GB (1999) Overexpression of Edg-2/vzg-1 induces apoptosis and anoikis in ovarian cancer cells in a lysophosphatidic acid-independent manner. Clin Cancer Res 5:4308–4318

Furuta D, Yamane M, Tsujiuchi T, Moriyama R, Fukushima N (2012) Lysophosphatidic acid induces neurite branch formation through LPA3. Mol Cell Neurosci 50:21–34

Geraldo LHM, Spohr TCLS, Amaral RFD, Fonseca ACCD, Garcia C, Mendes FA, Freitas C, dosSantos MH, Lima FRS (2021) Role of lysophosphatidic acid and its receptors in health and disease: novel therapeutic strategies. Signal Trandsuct Target Ther 6:45

Gerrard JM, Kingdom SE, Peterson DA, Peller J, Krantz KE, White JG (1979) Lysophosphatidic acids. Influence on platelet aggregation and intracellular calcium. Am J Pathol 96:423–438

Hamilton G, Rath BA (2014) A short update on cancer chemoresistance. Wine Med Wochenschr 164:456–460

Hayashi M, Okabe K, Kato K, Okumura M, Fukui R, Fukushima N, Tsujiuchi T (2012) Differential function of lysophosphatidic acid receptors in cell proliferation and migration of neuroblastoma cells. Cancer Lett 326:91–96

Hermann PC, Huber SL, Herrler T, Aicher A, Ellwart JW, Guba M, Bruns CJ, Heeschen C (2007) Distinct populations of cancer stem cells determine tumor growth and metastatic activity in human pancreatic cancer. Cell Stem Cell 1:313–323

Honoki K, Fujii H, Kubo A, Kido A, Mori T, Tanaka Y, Tsujiuchi T (2010) Possible involvement of stem-like populations with elevated ALDH1 in sarcomas for chemotherapeutic drug resistance. Oncol Rep 24:501–505

Hu Y-L, Tee M-K, Goetzl EJ, Auersperg N, Mills GB, Ferrara N, Jaffe RB (2001) Lysophosphatidic acid induction of vascular endothelial growth factor expression in human ovarian cancer cells. J Natl Cancer Inst 93:762–768

Huang RX, Zhou PK (2020) DNA damage response signaling pathways and target for radiotherapy sensitization in cancer. Signal Transduct Target Ther 5:60

Huang W-H, Chang M-C, Tsai K-S, Hung M-C, Chen H-L, Hung S-C (2013) Mesenchymal stem cells promote growth and angiogenesis of tumors in mice. Oncogene 32:4343–4354

Insel PA, Zhang L, Murray F, Yokouchi H, Zambon AC (2012) Cyclic AMP is both a pro-apoptotic and anti-apoptotic second messenger. Acta Physiol 204:277–287

Ishii S, Noguchi K, Yanagida K (2009) Non-edg family lysophsphatidic acid (LPA) receptors. Prostaglandins Other Lipid Mediat 89:57–65

Ishii S, Hirane M, Fukushima K, Tomimatsu A, Fukushima N, Tsujiuchi T (2015) Diverse effects of LPA_4, LPA_5 and LPA_6 on the activation of tumor progression in pancreatic cancer cells. Biochem Biophys Res Commun 461:59–64

Jeon ES, Moon HJ, Lee MJ, Song HY, Kim YM, Cho M, Suh D-S, Yoon M-S, Chang CL, Jung JS, Kim JH (2008) Cancer-derived lysophosphatidic acid stimulates differentiation of human mesenchymal stem cells to myofibroblast-like cells. Stem Cells 26:789–797

Jeon ES, Heo SC, Lee IH, Choi YJ, Park JH, Choi KU, Park DY, Suh DS, Yoon MS, Kim JH (2010) Ovarian cancer-derived lysophosphatidic acid stimulates secretion of VEGF and stromal cell-derived factor-1α from human mesenchymal stem cells. Exp Mol Med 42:280–293

Jinno N, Yoshida M, Hayshi K, Naitho I, Hori Y, Natsume M, Kato A, Kachi K, Asano G, Atsuta N, Sahashi H, Kataoka H (2021) Autotaxin in ascites projotes peritoneal dissemination in pancreatic cancer. Cancer Sci 112:668–678

Kathawala RJ, Gupta P, Ashby CR Jr, Chen Z-S (2015) The modulation of ABC transporter-mediated multidrug resistance in cancer: a review of the past decade. Drug Resist Updat 18:1–17

Kato K, Fukui R, Okabe K, Tanabe E, Kitayoshi M, Fukushima N, Tsujiuchi T (2012) Constitutively active lysophosphatidic acid receptor-1 enhances the induction of matrix metalloptoteinase-2. Biochem Biophys Res Commun 417:790–793

Kessenbrock K, PlaksV, Werb Z (2010) Matrix metalloproteinases: regulators of the tumor microenvironment. Cell 141:52–67

Kitayama J, Shida D, Sako A, Ishikawa M, Hama K, Aoki J, Arai H, Nagawa H (2004) Over-expression of lysophosphatidic acid receptor-2 in human invasive ductal carcinoma. Breast Cancer Res 6:R640–R646

Komachi M, Tomura H, Malchinkhuu E, Tobo M, Mogi C, Yamada T, Kimura T, Kuwabara A, Ohta H, Im D-S, Kurose H, Takeyoshi I, Sato K, Okajima F (2009) LPA1 receptors mediate stimulation, whereas LPA2 receptors mediate inhibition, of migration of pancreatic cancer cells in response to lysophosphatidic acid and malignant ascites. Carcinogenesis 30:457–465

Kurisu R, Takamoto M, Minami K, Ueda N, Yamada M, Shima N, Otani T, Sakai Y, Kondo D, Tsujiuchi T (2022) Effects of lysophosphatidic acid (LPA) signaling via LPA receptors on cellular functions associated with ATP reduction in osteosarcoma cells treated with ethidium bromide. J Bioenerg Biomemr 54:109–117

Leblanc R, Peyruchaud O (2015) New insights into the autotaxin/LPA axis in cancer development and metastasis. Exp Cell Res 333:183–189

Leve F, Peres-Moreira RJ, Binato R, Abdelhey E, Morgado-Díaz JA (2018) LPA induces colon cancer cell proliferation through a cooperation between the ROCK and STAT-3 pathways. PLoS ONE 10:e0139094

Lin M-E, Herr DR, Chun J (2010) Lysophosphatidic acid (LPA) receptors: signaling properties and disease relevance. Prostaglandins Other Lipid Mediat 91:130–138

Minami K, Ueda N, Maeda H, Ishimoto K, Otagaki S, Tsujiuchi T (2019) Modulation of chemoresistance by lysophosphatidic acid (LPA) signaling through LPA_5 in melanoma cells treated with anticancer drugs. Biochem Biophys Res Commun 517:359–363

Minami K, Ueda N, Ishimoto K, Tsujiuchi T (2020a) LPA_5-mediated signaling induced by endothelial cells and anticancer drug regulates cellular functions of osteosarcoma cells. Exp Cell Res 388:111813

Minami K, Ueda N, Ishimoto K, Kurisu R, Takamoto M, Ikeda H, Tsujiuchi T (2020b) Cooperation of G12/13 and Gi proteins via lysophosphatidic acid receptor-2 (LPA_2) signaling enhances cancer cells survival to cisplatin. Biochem Biophys Res Commun 542:427–432

Minami K, Ueda U, Ishimoto K, Kurisu R, Takamoto M, Ikeda H, Tsujiuchi T (2021) Roles of endothelial cells in the regulation of cell motility via lysophosphatidic acid receptor-2 (LPA_2) and LPA_3 in osteosarcoma cells. Exp Mol Pathol 118:104596

Mokady D, Meiri D (2015) RhoGTPases - A novel link between cytoskeleton organization and cisplatin resistance. Drug Resist Updat 19:22–32

Morrison R, Schleicher SM, Sun Y, Niermann KJ, Kim S, Sparatt DE, Chung CH, Lu B (2011) Targeting the mechanisms of resistance to chemotherapy and radiotherapy with the cancer stem cell hypothesis. J Oncol 2011:941876

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

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

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

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

Okuda A, Takai M, Kurisu R, Takamoto M, Ikeda H, Tsujiuchi T (2023) Roles of lysophosphatidic acid (LPA) receptor-2 (LPA_2) in the regulation of cellular responses induced by X-ray irradiation and hydrogen peroxide in pancreatic cancer cells. Int J Radiat Biol in press

Pasternack SM, von Kügelgen I, Aboud KA, Lee YA, Rüschendorf F, Voss K, Hillmer AM, Molderings GJ, Franz T, Ramirez A, Nürnberg P, Nöthen MM, Betz RC (2008) G protein-coupled receptor P2Y5 and its ligand LPA are involved in maintenance of human hair growth. Nat Genet 40:329–334

Ptaszynska MM, Pendrak ML, Stracke ML, Roberts DD (2010) Autotaxin signaling via lysophosphatidic acid receptors contributes to vascular endothelial growth factor-induced endothelial cell migration. Mol Cancer Res 8:309–321

Samadi N, Bekele R, Capatos D, Venkatraman G, Sariahmetoglu M, Brindley DN (2011) Regulation of lysophosphatidate signaling by autotaxin and lipid phosphate phosphatases with respect to tumor progression, angiogenesis, metastasis and chemo-resistance. Biochimie 93:61–70

Sano T, Baker D, Virag T, Wada A, Yatomi Y, Kobayashi T, Igarashi Y, Tigyi G (2002) Multiple mechanisms linked to platelet activation result in lysophosphatidic acid and sphingosine 1-phosphate generation in blood. J Biol Chem 277:21197–21206

Sau A, Tregno FP, Valentino F, Federici G, Caccuri AM (2010) Glutathione transferases and development of new principles to overcome drug resistance. Arch Biochem Biophys 500:116–122

Schulte KM, Beyer A, Köhrer K, Oberhäuser S, Röher HD (2001) Lysophosphatidic acid, a novel lipid growth factor for human thyroid cells: over-expression of the high-affinity receptor edg4 in differentiated thyroid cancer. Int J Cancer 92:249–256

Seo EJ, Kwon YW, Jang IH, Kim DK, Lee SI, Choi EJ, Kim K-H, Suh D-S, Lee JH, Chou KU, Lee JW, Mok HJ, Kim KP, Matsumoto H, Aoki J, Kim JH (2016) Autotaxin regulates maintenance of ovarian cancer stem cells through lysophosphatidic acid-mediated autocrine mechanism. Stem Cells 34:551–564

Shida D, Kitayama J, Yanaguchi H, Okaji Y, Tsuno NH, Watanabe T, Takuwa Y, Nagawa H (2003) Lysophosphatidic acid (LPA) enhances the metastatic potential of human colon carcinoma DLD1 cells through LPA1. Cancer Res 63:1706–1711

Shida D, Kitayama J, Yamaguchi H, Hama K, Aoki J, Arai H, Yamashita H, Mori K, Sako A, Konishi T, Watanabe T, Sakai T, Suzuki R, Ohta H, Takuwa Y, Nagawa H (2004a) Dual mode regulation of migration by lysophosphatidic acid in human gastric cancer cells. Exp Cell Res 301:168–178

Shida D, Watanabe T, Aoki J, Hama K, Kitayama J, Sonoda H, Kishi Y, Yamaguchi H, Sasaki S, Sako A, Konishi T, Arai H, Nagawa H (2004b) Aberrant expression of lysophosphatidic acid (LPA) receptors in human colorectal cancer. Lab Invest 84:1352–1362

Shimomura Y, Garzon MC, Kristal L, Shapiro L, Christiano AM (2009) Autosomal recessive wooly hair with hypotrichosis caused by a novel homozygous mutation in the P2RY5 gene. Exp Dermatol 18:218–221

Steegborn C (2014) Structure, mechanisms, and regulation of soluble adenylyl cyclases – similarities and differences to transmembrane adenylyl cyclases. Biochim Biophys Acta 1842:2535–2547

Stoddard NC, Chun J (2015) Promising pharmacological directions in the world of lysophosphatidic acid signaling. Biomol Ther 23:1–11

Stracke ML, Krutzsch HC, Unsworth EJ, Arestad A, Cioce V, Schiffmann E, Liotta LA (1992) Identification, purification, and partial sequence analysis of autotaxin, a novel motility-stimulating protein. J Biol Chem 267:2524–2529

Takagi S, Sasaki Y, Koike S, Takemoto A, Seto Y, Haraguchi M, Ukaji T, Kawaguchi T, Sugawara M, Saito M, Funauchi Y, Ae K, Matcumoto S, Fujita N, Katayama R (2021) Platelet-derived

lysophosphatidic acid mediated LPAR1 activation as a therapeutic target for osteosarcoma metastasis. Oncogene 40:5548–5558

Takahashi K, Fukushima K, Onishi Y, Fukushima N, Honoki K, Tsujiuchi T (2017a) Lysophosphatidic acid (LPA) signaling via LPA_4 and LPA_6 negatively regulates cell motile activities of colon cancer cells. Biochem Biophys Res Commun 483:652–657

Takahashi K, Fukushima K, Fukushima N, Honoki K, Tsujiuchi T (2017b) Enhanced cellular functions through induction of LPA_2 by cisplatin in fibrosarcoma HT1080 cells. Mol Cell Biochem 431:29–35

Takahashi K, Fukushima K, Otagaki S, Ishimoto K, Minami K, Fukushima N, Honoki K, Tsujiuchi T (2018a) Effects of LPA_1 and LPA_6 on the regulation of colony formation activity in colon cancer cells treated with anticancer drugs. J Recept Signal Transduct Res 38:71–75

Takahashi K, Fukushima K, Tanaka K, Minami K, Ishimoto K, Otagaki S, Fukushima N, Honoki K, Tsujiuchi T (2018b) Involvement of LPA signaling via LPA receptor-2 in the promotion of malignant properties in osteosarcoma cells. Exp Cell Res 369:316–324

Takai M, Takauchi M, Kuribayashi M, Tsujiuchi T (2023) LPA receptor-mediated signaling regulates cell motility and survival to anticancer drug of pancreatic cancer cells under glucose-deprived and hypoxic conditions. Biochem Biophys Res Commun 661:21–27

Tanabe E, Kitayoshi M, Hirane M, Araki M, Dong Y, Fukushima N, Tsujiuchi T (2013) Downregulation of activation factors of endothelia and fibroblasts via lysophosphatidic acid signaling in a mouse lung cancer LL/2 cell line. J Recept Signal Transduct Res 33:286–290

Tokumura A, Fukuzawa K, Akamatsu Y, Yamada S, Suzuki T, Tsukatani H (1978) Identification of vasopressor phospholipid in crude soybean lecithin. Lipids 13:468–472

Tsujino M, Fujii M, Okabe K, Mori T, Fukushima N, Tsujiuchi T (2010) Differential expressions and DNA methylation patterns of lysophosphatidic acid receptor genes in human colon cancer cells. Virchows Arch 457:669–676

Tsujiuchi T, Araki M, Hirane M, Dong Y, Fukushima N (2014) Lysophosphatidic acid receptors in cancer pathobiology. Histol Histopathol 29:313–321

Tsukamoto S, Honoki K, Fujii H, Tohma Y, Kido A, Mori T, Tsujiuchi T, Tanaka Y (2012) Mesenchymal stem cells promote tumor engraftment and metastatic colonization in rat osteosarcoma model. Int J Oncol 40:163–169

Ueda N, Minami K, Ishimoto K, Tsujiuchi T (2020) Effects of lysophosphatidic acid (LPA) receptor-2 (LPA_2) and LPA_3 on the regulation of chemoresistance to anticancer drug in lung cancer cells. Cell Signal 69:109551

van Meeteren LA, Moolenaar WH (2007) Regulation and biological activities of the autotaxin-LPA axis. Prog Lipid Res 46:145–160

Visvader JE, Lindeman GJ (2008) Cancer stem cells in solid tumours: accumulating evidence and unresolved questions. Nat Rev Cancer 8:755–768

Xu Y, Gaudette DC, Boynton JD, Frankel A, Fang X-J, Sharme A, Hurteau J, Casey G, Goodbody A, Mellors A, Holub BJ, Mills B (1995) Characterization of an ovarian cancer activating factor in ascites from ovarian cancer patients. Clin Cancer Res 1:1223–1232

Yamada T, Furukawa M, Hotta M, Yamasaki A, Honoki K, Fukushima N, Tsujiuchi T (2009) Mutations of lysophosphatidic acid receptor-1 gene during progression of lung tumors in rats. Biochem Biophys Res Commun 378:424–427

Yu S, Murph MM, Lu Y, Liu S, Hall HS, Liu J, Stephens C, Fang X, Mills GB (2008) Lysophosphatidic acid receptors determine tumorigenicity and aggressiveness of ovarian cancer cells. J Natl Cancer Inst 100:1630–1642

Yung YC, Stoddard N, Chun J (2014) LPA receptor signaling: pharmacology, physiology, and pathophysiology. J Lipid Res 55:1192–1214

Zhang H, Kong Q, Wang J, Jiang Y, Hua H (2020) Complex roles of cAMP-PKA-CREB signaling in cancer. Exp Hematol Oncol 9:32