Review

Lysophosphatidic acid receptors in cancer pathobiology

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Summary. Lysophosphatidic acid (LPA) receptors (LPA_1 to LPA_6) are G protein-coupled transmembrane and mediate a variety of biological responses through the binding of LPA, such as cell proliferation, migration, morphogenesis and differentiation. Previously, high secretion levels of LPA were found in blood and ascites from patients with aggressive ovarian cancer. So far, numerical studies have demonstrated that LPA signaling via LPA receptors contributes to the acquisition of malignant potency by several cancer cells. Moreover, genetic and epigenetic alterations of LPA receptor genes have been detected in cancer cells. Therefore, it is suggested that LPA signaling may be a target molecule for the establishment of chemoprevention agents in clinical cancer approaches. Here, we review the current knowledge for the biological roles of LPA signaling via LPA receptors in the pathogenesis of cancer cells.

Key words: LPA, LPA receptor, Cancer, Cell function, Gene alteration

Introduction

Lysophosphatidic acid (LPA) is a bioactive lipid mediator. It interacts with specific G protein-coupled transmembrane receptors, which are identified as LPA receptor-1 (LPA_1), LPA_2, LPA_3, LPA_4, LPA_5 and LPA_6. LPA signaling via LPA receptors indicates a wide range of cellular responses, such as cell proliferation, migration, morphogenesis, differentiation and protection from apoptosis. However, it has been considered that the individual LPA receptors have diverse cellular effects, depending on the cell types involved (Contos et al., 2000; Ishii et al., 2004, 2009; Choi et al., 2010).

In 1995, Xu et al. found that high concentrations of LPA were contained in blood and ascites from patients with aggressive ovarian cancer (Xu et al., 1995). So far, numerical studies have evaluated whether LPA receptors are involved in the pathogenesis of cancer cells as well as LPA per se. Subsequently, it has been demonstrated that LPA signaling via LPA receptors contributes to the acquisition of malignant potency by several cancer cells, including cell growth, motility, invasion, tumorigenicity, angiogenesis, metastasis and drug resistance (Lin et al., 2010). Furthermore, we detected that genetic and epigenetic alterations of LPA receptor genes occur in cancer cells (Tsujiuchi et al., 2011). Therefore, it is suggested that LPA signaling may be a target molecule for novel chemoprevention agents in clinical cancer approaches.

Recently, the functional analyses using LPA receptor expressing and knockdown cells have revealed that each LPA receptor acts as a positive or negative regulator of cellular functions, depending on the types of cancer cells.

In this review, we here provide updated findings for the biological roles of LPA receptors in the pathogenesis of cancer cells.

LPA and LPA receptors

LPA is an extracellular signaling lipid, structured by a glycerol, a fatty acid and a phosphate. Extracellular LPA is produced via two independent pathways;

autotoxin-mediated conversion of lysophosphatidyl-choline and membrane-bound phosphatidic acid-preferring phospholipase A1-mediated conversion of PA (Aoki et al., 2008; Choi and Chun, 2013). It interacts with G protein-coupled transmembrane LPA receptors. So far, at least six types of LPA receptors have been identified, such as LPA_1/EDG2, LPA_2/EDG4, LPA_3/EDG7, LPA_4/P2Y9/GPR23, LPA_5/GPR92 and LPA_6/P2Y5. In a recent report, GPR87 has been additionally proposed to be a candidate as a new LPA receptor. The expression patterns of LPA receptors are dependent on the cell types. While normal tissues ubiquitously expressed LPA_1, the expression levels of other LPA receptors are varied (Contos et al., 2000; Ishii et al., 2004; Tabata et al., 2007).

LPA receptors couple with individual sets of G proteins (G_i, G_q, and G12/13) and LPA signaling via LPA receptors indicates a variety of cellular responses, including cell growth, migration, differentiation, morphogenesis and protection from apoptosis. However, the biological effects of each LPA receptor to LPA are not functionally equivalent. For example, LPA_1 and LPA_2 increase cell growth activity, intracellular calcium mobilization, phospholipase C activation and adenylyl cyclase inhibition, while knockout mice of LPA_1 and LPA_2 revealed some different phenotypes. Almost all LPA receptor subtypes mediate LPA-induced neurite retraction and growth cone collapse, but LPA_3 does not (Ishii et al., 2000; Contos et al., 2002; Fukushima, 2004). On the other hand, LPA_3 stimulates axon branching through the activation of Gq subunit and Rnd2 in neuronal cells (Furuta et al., 2012). In recent studies, it has been demonstrated that LPA receptors are involved in the pathogenesis of several diseases, including cancer (Lin et al., 2010).

The role of LPA receptors in cellular functions of cancer cells

Cell proliferation, motility and invasion

Each LPA receptor shows different cellular effects on cell proliferation, motility and invasion in cancer cells. In highly *LPAR1*-expressing ovarian cancer cells, LPA indicated the inhibitory effects on cell proliferation and induced cell death through apoptosis and anoikis (Furui et al., 1999; Fang et al., 2002). In colon cancer cells, LPA stimulated cell proliferation, migration and adhesion of *LPAR1*-expressing cells. In contrast, LPA did not affect cell migration and adhesion of *LPAR2*-expressing cells, whereas it increased cell proliferation (Shida et al., 2003). In gastric cancer cells, LPA markedly stimulated cell migration of *LPAR1*-expressing cells, but not in *LPAR2*-expressing cells (Shida et al., 2004a). These findings suggest that LPA_1 may act as a positive regulator of cancer cell migration. On the other hand, it has been shown that LPA signaling via LPA_3 mainly enhances cell migration of cancer cells.

Exogenous LPA_3 markedly stimulated cell migration and invasion of hepatoma and sarcoma cells (Tanabe et al., 2012; Okabe et al., 2013). Using a knockdown method by small interfering RNAs, it has been indicated that LPA_2 and LPA_3 elevated cell migration and invasion of ovarian cancer cells (Yu et al., 2008). Moreover, exogenous LPA_1 inhibited and LPA_3 enhanced cell migration of neuroblastoma and pancreatic carcinoma cells (Hayashi et al., 2012; Kato et al., 2012a). In contrast, exogenous LPA_3 inhibited cell migration of lung and colon cancer cells (Hayashi et al., 2011; Fukui et al., 2012a). In addition, LPA_5 stimulated cell proliferation and migration of lung and liver cancer cells (Okabe et al., 2011). It is unclear why each LPA receptor shows a different behavior in cellular functions of cancer cells. One possibility is that their diverse effects may be due to different expression patterns of LPA receptors in cancer cells. In fact, LPA receptors can form heterodimers with other receptors, resulting in novel signaling and different functional responses (Zaslavsky et al., 2006).

MMP activation

Matrix metalloproteinases (MMPs) are proteolytic enzymes and induce extracellular matrix degradation. It is widely accepted that MMPs play an important role in invasion and metastasis of tumor cells. In particular, MMP-2 and MMP-9 significantly contribute to the progression of cancer cells (Chen and Parks, 2009; Kessenbrock et al., 2010). In ovarian cancer cells, it has been reported that LPA promoted cell migration and invasion through the activation of MMP-2 (Fishman et al., 2001). Moreover, it stimulated cell invasion through a Ras/Rho/ROCK signaling and subsequent MMP-9 production (Jeong et al., 2012). In human hepatocellular carcinoma (HCC) cells, LPA signaling via LPA_1 enhanced invasive activity by MMP-9 secretion (Park et al., 2011). In contrast, LPA_3 induced proMmp-9 activation in rat HCC cells which unexpressed LPA_1 (Okabe et al., 2013). Interestingly, mutated LPA_1 significantly enhanced Mmp-2 expression and activation, while the expression and activation were at the same levels in other LPA receptors (Kato et al., 2012b).

Tumorigenicity

Some investigations have assessed whether LPA receptors contribute to tumorigenicity in cancer cells. In a mouse xenograft model, *LPAR2* or *LPAR3*-expressing cells increased primary tumor size, ascites volume and metastatic potency to distant organs, and reduced the survival rate of mice (Yu et al., 2008). Using colony assay, LPA_3 formed large sized colonies in HCC and neuroblastoma cells. Mutated LPA_1 also formed large sized colonies in neuroblastoma cells (Hayashi et al., 2012; Okabe et al., 2013).

Angiogenesis

Angiogenesis is defined as the important process of producing new blood vessels from the existing vasculature network and activates invasive and metastatic potency of cancer cells (Folkman, 1971). Functionally, angiogenesis is regulated by several growth factors, such as vascular endothelial growth factors (VEGFs). VEGFs are produced by tumor cells *per se* and promote angiogenesis. Conversely, its suppression can lead to the inhibition of tumor growth (Kim et al., 1993; Ferrara et al., 2003).

It has been reported that LPA induced mRNA expression and protein secretion of VEGF in human ovarian cancer cells, demonstrating that LPA_2 may be mainly involved in the activation of VEGF expression (Goetzl et al., 1999; Hu et al., 2001). Other investigators indicated that LPA_2 and LPA_3 expression levels were correlated with the induction of VEGF expression in ovarian cancer tissues (Fujita et al., 2003). Furthermore, a recent study showed that knockdown of LPA_2 or LPA_3 suppressed the production of VEGF in ovarian cancer cells (Yu et al., 2008). In colon cancer cells, LPA induced the secretion of angiogenic factors through LPA_1 and LPA_2 (Shida et al., 2003). On the other hand, it has been reported that LPA signaling via LPA receptors stimulates cell motile activity of endothelial cells. When endothelial cells were cultured with conditioned medium from exogenous LPA receptor expressing neuroblastoma cells, LPA_1 and LPA_3 stimulated the cell motile activities of endothelial cells. Moreover, mutated LPA_1 strongly enhanced the cell motile activities of endothelial cells. The elevated cell motile activities of endothelial cells were correlated with the expression levels of VEGF genes (Kitayoshi et al., 2012). In contrast, LPA_3 inhibited angiogenesis in mouse lung cancer LL/2 cells (Tanabe et al., 2013).

Multidrug resistance

Multidrug resistance is a phenomenon of simultaneous resistance to structurally and functionally unrelated anticancer drugs in cancer cells. The important mechanisms underlying the acquisition of multidrug resistance is the activation of efflux transporter proteins, such as P-glycoprotein which is encoded by multidrug resistance (MDR) genes (Szakács et al., 2006). Moreover, the induction of glutathione S-transferases (GSTs) which represent a major family of detoxification enzymes is also well known (Sau et al., 2010). In ovarian cancer cells, *LPAR1*-expressing cells indicated drug resistance to cisplatin (CDDP) with low cell proliferation activity, in comparison with *LPAR1*-unexpressing cells. Hever, when LPA_1 was exogenously expressed in *LPAR1*-unexpressing cells, it did not significantly alter CDDP sensitivity (Furui et al., 1999). In HCC and mammary tumor cells, exogenous LPA_3 exhibited high cell survival to CDDP and doxorubicin (DOX) treatment, which were correlated with the induction of *Mdr1a, Mdr1b* and *Gstp1* genes (Fukui et al., 2012b; Okabe et al., 2013).

LPA receptor gene alterations in cancer cells and tissues

It is known that high concentrations of LPA are contained in plasma and ascitic fluid from patients with widespread ovarian cancer (Xu et al., 1995; Choi et al., 2010). LPA per se enhances malignant potencies of cancer cells, including cell proliferation, migration, invasion and production of angiogenic factors (Fang et al., 2000; Aoki et al., 2008; Choi et al., 2013). Moreover, numerical studies have demonstrated that alteration of LPA receptors is involved in the pathogenesis of cancer cells. Altered expression and DNA methylation patterns of LPA receptor genes were found in human and rodent cancer cells. Mutations of LPA receptor genes occurred in rodent carcinogenesis models, similar to the case for human cancer cells.

Genetic alterations

Aberrant LPA receptor gene expressions

Since the distribution of LPA receptor expressions is various in normal tissues, it is suggested that these receptors indicate the different biological effects regarding LPA (Ishii et al., 2004). In human ovarian, colon and gastric cancer cells, a variety of *LPAR1* and *LPAR2* gene expression levels were shown by northern blot analyses (Furui et al., 1999; Pustilnik et al., 1999; Shida et al., 2003, 2004a). Overexpression levels of *LPAR2* gene were detected in papillary and follicular thyroid cancers, in comparison with those in normal thyroid tissues, but not *LPAR1* gene (Schulte et al., 2001). The expression levels of *LPAR2* gene in human breast cancers were significantly higher than those in normal mammary grand, while those of *LPAR1* and *LPAR3* genes were not. Immunohistochemical studies confirmed the positive staining of LPA_2 protein in cancer cells. In particular, the increased expression levels of the *LPAR2* gene were shown in postmenopausal patients with breast cancers, in comparison with premenopausal cases (Kitayama et al., 2004). Shida et al. reported that colorectal cancers expressed *LPAR1* gene at a lower level and *LPAR2* gene at a higher level, as compared with normal tissues, while *LPAR3* gene expression levels remained unchanged (Shida et al., 2004b). In addition, aberrant expression levels of LPA receptor genes were found in rat lung and liver tumors induced by chemical carcinogens (Tsujiuchi et al., 2006a).

Mutations of LPA receptor genes

Human cancer cells. To look for mutations of LPA receptor genes in cancer cells, polymerase chain reaction (PCR) - single strand conformation polymorphism (SSCP) analysis was performed (Murakami et al., 1991).

In colon cancer DLD1, SW480, HCT116, CaCo-2, SW48, and LoVo cells, two out of 6 cells indicated *LPAR2* and/or *LPAR4* gene mutations, while no mutation of *LPAR1, 3,* and *5* genes was detected. DLD1 cells harbored a GTG to GTA (Val to Val) transition at codon 136 and a CGC to CAC (Arg to His) transition at codon 146 in *LPAR2* gene, and a CGC to CAC (Arg to His) transition at codon 232 in *LPAR4* gene. SW48 cells also harbored a GTG to GTA (Val to Val) transition at codon 136 and a CCC to CTC (Pro to Leu) transition at codon 230 in *LPAR2* gene (Tsujino et al., 2010).

In other cancer cells, Okabe et al. looked for the presence of mutations in LPA receptor genes in osteosarcoma MG63, fibrosarcoma HT1080, lung adenocarcinoma A549, breast carcinoma MCF-7 and melanoma G-361 cells. However, *LPAR1* and *LPAR3* gene mutations were only found in MG63 cells. These mutation patterns were a CGC to CGT (Arg to Arg) transition at codon 314 in *LPAR1* gene, and a GCG to GTG (Ala to Val) transition at codon 247 in *LPAR3* gene (Okabe et al., 2010a) (Table 1).

Rodent cancers. Frequent mutations of *Lpar1* gene were detected in experimental studies. The mutation analyses for LPA receptor genes during rat lung carcinogenesis induced by N-nitrosobis(2-hydroxypropyl)amine were performed. The frequency of *Lpar1* mutations was 16.7% in adenomas and 41.2% in adenocarcinomas, but not in alveolar hyperplasias (Yamada et al., 2009). In contrast, no mutation of *Lpar2, Lpar3, Lpar4* and *Lpar5* genes was found in adenocarcinomas (Wakabayashi et al., 2010). For HCCs, tumors were induced by exogenous and endogenous hepatocarcinogenesis models. The former is the model for induction of HCCs by N-nitrosodiethylamine (DEN), which is one of the most well-known liver carcinogens (Ohashi et al., 1996). The latter, endogenous carcinogenesis means that tumors are induced by endogenous changes that occur without any established carcinogen exposure, and prolonged feedings of a choline-deficient L-amino acid-defined (CDAA) diet can induce rat HCCs (Nakae et al., 1992). Mutations of the *Lpar1* gene were detected 46.7% in HCCs by DEN and 41.7% in HCCs by the CDAA diet (Obo et al., 2009). In contrast, no mutation of the *Lpar5* was found in HCCs induced by DEN (Okabe et al., 2011). In hamster pancreatic duct adenocarcinomas (PDAs) induced by N-nitrosobis(2-oxopropyl)amine, only 10% of PDAs harbored missense mutations of the *Lpar1* gene (Tsujiuchi et al., 2009). Taken together, these results suggest that LPA signaling via mutated LPA_1 is mainly involved in the pathogenesis of rat lung and liver tumors (Table 2).

Pattern and location of mutations

Pattern of mutations. In DLD1 and SW48 cells, three

Table 1. Mutations of LPA receptor genes in human cancer cells.

Receptors	Cells	Mutation patterns	Refs.
LPA_1	MG62	314 CGC to CGT (Arg to Arg)	Okabe et al., 2010a
LPA_2	DLD1	136 GTG to GTA (Val to Val), 146 CGC to CAC (Arg to His)	Tsujino et al., 2010
	SW48	136 GTG to GTA (Val to Val), 230 CCC to CTC (Pro to Leu)	Tsujino et al., 2010
LPA_3	MG63	247 GCG to GTG (Ala to Val)	Okabe et al., 2010a
LPA_4	DLD1	232CGC to CAC (Arg to His)	Tsujino et al., 2010

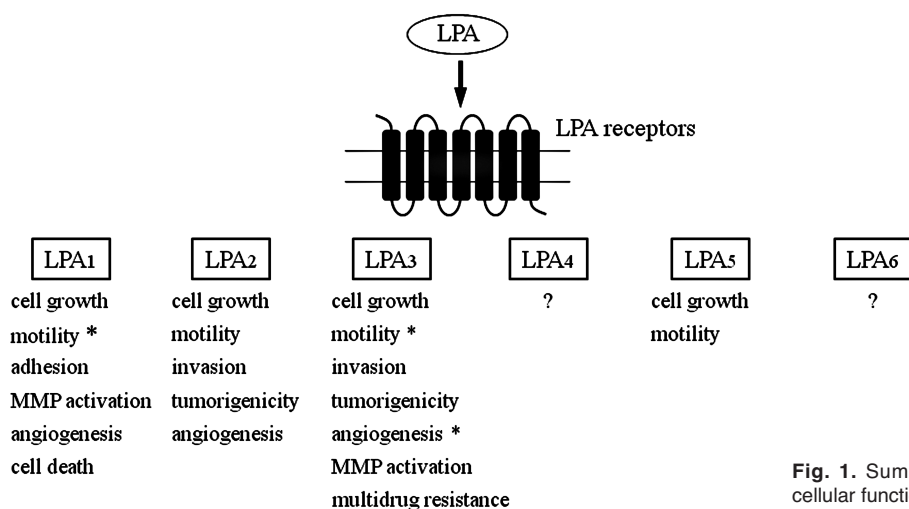| LPA1	LPA2	LPA3	LPA4	LPA5	LPA6
cell growth	cell growth	cell growth	?	cell growth	?
motility *	motility	motility *		motility	
adhesion	invasion	invasion			
MMP activation	tumorigenicity	tumorigenicity			
angiogenesis	angiogenesis	angiogenesis *			
cell death		MMP activation			
		multidrug resistance			

Fig. 1. Summary for the effects of each LPA receptor on cellular functions in cancer cells. * : stimulate or inhibit.

mutations of *LPAR2* and one of *LPAR4* were all G/C to A/T transitions (Tsujino et al., 2010). In MG63 cells, two mutations of *LPAR1* and *LPAR3* were all C/G to T/A transitions (Okabe et al., 2010a). In contrast, a variety of *Lpar1* mutations were detected in lung, liver and pancreatic tumors of rodents. Among 17 mutations in those tumors, 10 cases were T/A to C/G transitions, four G/C to T/A transversions, two G/C to A/T transitions and a C/G to T/A transition. Interestingly, 5 mutations in rat HCCs by the CDAA diet were all T/A to C/G transitions (Yamada et al., 2009; Obo et al., 2009; Tsujiuchi et al., 2009).

G/C to A/T transition is one specific mutation pattern induced by nitroso-compounds (Tsutsumi et al., 1993; Jiao et al., 1996; Kitada et al., 1996). Moreover, it is known that G/C to T/A and A/T to C/G transversions and T/A to C/G transition are induced by 8-hydroxyguanine in Escherichia coli and mammalian cells (Moriya et al., 1991; Kamiya et al., 1995; Wang et al., 1998). The oxy radical-mediated DNA damage generates several DNA adducts, including 8-hydroxyguanine and 8-hydroxyadenine (Malins et al., 1990). Therefore, it seems that *Lpar1* gene mutations detected in rodent tumors may be due to oxidative DNA damage rather than nitroso-compounds per se. However, it is unclear why G/C is a target nucleotide for LPA

Table 2. Mutations of LPA receptor genes in rodent tumors.

Receptors	Tissues	Species	Incidence (%)	Refs.
LPA$_1$	Lung adenomas	rat	2/12 (16.7)	Yamada et al., 2009
	Lung adenocarcinomas	rat	7/17 (41.2)	Yamada et al., 2009
	HCCs	rat	12/27 (44.4)	Obo et al., 2009
	PDAs	hamster	1/10 (10.0)	Tsujiuchi et al., 2009
LPA$_2$	Lung adenocarcinomas	rat	N.D.	Wakabayashi et al., 2010
LPA$_3$	Lung adenocarcinomas	rat	N.D.	Wakabayashi et al., 2010
LPA$_4$	Lung adenocarcinomas	rat	N.D.	Wakabayashi et al., 2010
LPA$_5$	Lung adenocarcinomas	rat	N.D.	Wakabayashi et al., 2010
	HCCs	rat	N.D.	Obo et al., 2009

Table 3. DNA methylation status of LPA receptor genes in human colon cancer cells.

Cells	LPA receptors			
	LPA$_1$	LPA$_2$	LPA$_3$	LPA$_5$
DLD1	unmethylated	unmethylated	highly methylated	highly methylated
SW48	unmethylated	unmethylated	highly methylated	moderately methylated
HTC116	unmethylated	unmethylated	unmethylated	weakly methylated
SW480	unmethylated	unmethylated	moderately methylated	weakly methylated
CaCo2	unmethylated	unmethylated	moderately methylated	highly methylated
LoVo	unmethylated	unmethylated	highly methylated	moderately methylated

Tsujino et al., 2010.

Table 4. DNA methylation status of LPA receptor genes in rodent cancer cells.

Cells	Species	LPA receptors			Refs.
		LPA$_1$	LPA$_3$	LPA$_5$	
LL/2	mouse	unmethylated	highly methylated	N.E.	Okabe et al., 2010b
B16F0	mouse	highly methylated	highly methylated	N.E.	Okabe et al., 2010b
FM3A	mouse	highly methylated	highly methylated	N.E.	Okabe et al., 2010b
L1210	mouse	highly methylated	highly methylated	N.E.	Okabe et al., 2010b
RH7777	rat	highly methylated	highly methylated	unmethylated	Tsujiuchi et al., 2006b; Okabe et al., 2011, 2013
B103	rat	highly methylated	highly methylated	highly methylated	Tsujiuchi et al., 2006b; Hayashi et al., 2011; Okabe et al., 2011
COS	rat	unmethylated	moderately methylated	highly methylated	Tsujiuchi et al., 2006b; Hayashi et al., 2011; Okabe et al., 2011
RLCNR	rat	unmethylated	highly methylated	weakly methylated	Tsujiuchi et al., 2006b; Hayashi et al., 2011; Okabe et al., 2011
C6	rat	N.E.	weakly methylated	highly methylated	Tsujiuchi et al., 2006b; Hayashi et al., 2011; Okabe et al., 2011
MFH	rat	unmethylated	N.E.	N.E.	Tsujiuchi et al., 2006b

N.E.: not examined.

receptor gene mutations in human cancer cells.

Location of mutations. In colon cancer cells, three mutations are detected at the putative intracellular domain of LPA receptors (Tsujino et al., 2010). The *LPAR3* mutation is located within the 6th transmembrane domain in MG63 cells. (Okabe et al., 2010a). In rodent tumors, although *Lpar1* gene mutations occurred at several codons, missense mutations at codon 295 were frequently found; 44.4% in lung lesions induced by BHP, 25% in HCCs induced by DEN and the CDAA diet (Obo et al., 2009; Yamada et al., 2009). The biological significance of mutations in codon295 is unknown. However, it is adjacent to Lys294, which is one of the critical residues for ligand recognition or binding in the putative 7th transmembrane domain of LPA_1 (Sardar et al., 2002). It is possible that Lys294 play an important role in LPA binding and receptor activation. In fact, the artificial replacement of Lys294 with Ala could result in increased LPA response, suggesting that these amino acids may play an important role in LPA binding and subsequent receptor activation (Valentine et al., 2008). Shano et al. demonstrated that an artificial mutated LPA_1 was constitutively active and oncogenic (Shano et al., 2008).

Epigenetic alterations

DNA methylation is one of the epigenetic regulations for gene expression. It is widely accepted that loss of tumor suppressor gene expression is caused by aberrant DNA methylation of gene promoter regions in several tumors (Jones, 2002; Jones and Baylin, 2002, 2007). Recently, reduced expression levels of LPA receptor genes due to aberrant DNA methylation were detected in several cancer cells.

Human cancer cells

The expression levels and DNA methylation patterns of LPA receptor genes were profiled in DLD1, SW480, HCT116, CaCo-2, SW48, and LoVo cells. While all cells expressed *LPAR1, LPAR2* and *LPAR4* genes, the expression levels of *LPAR3* and *LPAR5* genes were various. The *LPAR3* gene was highly or moderately methylated in DLD1, SW480, CaCo-2, SW48, and LoVo cells, but unmethylated in HCT116 cells. The *LPAR5* gene was weakly methylated in SW480 and HCT116 cells, but highly or moderately methylated in other cells (Tsujino et al., 2010) (Table 3).

Rodent cancer cells

In mouse and rat cancer cells, DNA methylation status of LPA receptor genes was also profiled. Hypermethylation of the *Lpar1* gene was found in melanoma B16F0 cells, mammary carcinoma FM3A cells, and leukemia L1210 cells. The *Lpar3* gene was methylated in lung tumor LL/2, B16F0, FM3A, and

L1210 cells (Okabe et al., 2010b). In rat tumor cells, reduced expression levels of the *Lpar1* gene due to aberrant DNA methylation were detected in RH7777 and B103 cells, while normal liver and brain tissues expressed the *Lpar1* gene (Tsujiuchi et al., 2006b). Moreover, the *Lpar3* gene was highly methylated in RLCNR, B103 and RH7777 cells (Hayashi et al., 2011; Okabe et al., 2013). While normal lung and liver tissues were methylated, the *Lpar5* gene was weakly methylated or unmethylated in RLCNR and RH7777 cells (Okabe et al., 2011) (Table 4).In rat lung adenocarcinomas and HCCs induced by nitroso-compounds, five out of 6 lung adenocarcinomas (83.3%) and 4 out of 6 HCCs (66.7%) were unmethylated in the *Lpar5* gene, in comparison with normal lung and liver tissues which were methylated (Okabe et al., 2011).

Conclusion

In this review, we provide updated evidence for LPA signaling via LPA receptors and cancer cells. The possible involvement of LPA receptors in cellular functions of cancer cells are summarized in Fig.1. The central role of LPA signaling via LPA receptors in the pathogenesis of cancer is not yet resolved. However, it is worth considering that LPA signaling alteration frequently occurs in a variety of cancer cells and each LPA receptor acts as a positive or negative regulator of malignant properties. Therefore, it suggests that LPA signaling via LPA receptors may be a target molecule for the establishment of novel chemoprevention agents in clinical cancer approaches.

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