Summary. Lysophosphatidic acid (LPA) receptors (LPA₁ to LPA₆) 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.

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 (LPA₁), LPA₂, LPA₃, LPA₄, LPA₅ and LPA₆. 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 lysophosphatidylcholine and membrane-bound phosphatidic acid-prefering 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 LPA₁/EDG2, LPA₂/EDG4, LPA₄/EDG7, LPA₅/P2Y₉/GPR23, LPA₆/GPR92 and LPA₇/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 LPA₁, 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 (G₉, G₀, 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, LPA₁ and LPA₃ increase cell growth activity, intracellular calcium mobilization, phospholipase C activation and adenylyl cyclase inhibition, while knockout mice of LPA₁ and LPA₃ revealed some different phenotypes. Almost all LPA receptor subtypes mediate LPA-induced neurite retraction and growth cone collapse, but LPA₄ does not (Ishii et al., 2000; Contos et al., 2002; Fukushima, 2004). On the other hand, LPA₅ 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 LPA₁ may act as a positive regulator of cancer cell migration. On the other hand, it has been shown that LPA signaling via LPA₃ mainly enhances cell migration of cancer cells. Exogenous LPA₃ 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 LPA₆ and LPA₇ elevated cell migration and invasion of ovarian cancer cells (Yu et al., 2008). Moreover, exogenous LPA₃ inhibited and LPA₆ enhanced cell migration of neuroblastoma and pancreatic carcinoma cells (Hayashi et al., 2012; Kato et al., 2012a). In contrast, exogenous LPA₃ inhibited cell migration of lung and colon cancer cells (Hayashi et al., 2011; Fukui et al., 2012a). In addition, LPA₆ 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 LPA₁ enhanced invasive activity by MMP-9 secretion (Park et al., 2011). In contrast, LPA₃ induced proMMP-9 activation in rat HCC cells which unexpressed LPA₁ (Okabe et al., 2013). Interestingly, mutated LPA₁ 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, LPA₂ formed large sized colonies in HCC and neuroblastoma cells. Mutated LPA₁ 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 may be mainly involved in the activation of VEGF expression (Goetzl et al., 1999; Hu et al., 2001). Other investigators indicated that LPA2 and LPA3 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 LPA2 or LPA3 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 LPA1 and LPA3 (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, LPA1 and LPA3 stimulated the cell motile activities of endothelial cells. Moreover, mutated LPA1 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, LPA3 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 (DDP) with low cell proliferation activity, in comparison with LPAR1-unexpressing cells. However, when LPA1 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 LPA3 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 gland, while those of LPAR1 and LPAR3 genes were not. Immunohistochemical studies confirmed the positive staining of LPA2 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 (Tsujiiuchi 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 \textit{LPAR1} and/or \textit{LPAR4} gene mutations, while no mutation of \textit{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 \textit{LPAR2} gene, and a CGC to CAC (Arg to His) transition at codon 232 in \textit{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 \textit{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, \textit{LPAR1} and \textit{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 \textit{LPAR1} gene, and a CGC to GTG (Ala to Val) transition at codon 247 in \textit{LPAR3} gene (Okabe et al., 2010a) (Table 1).

\textbf{Rodent cancers.} Frequent mutations of \textit{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 \textit{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 \textit{Lpar2}, \textit{Lpar3}, \textit{Lpar4} and \textit{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-nitrosodimethylamine (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). In contrast, no mutation of the \textit{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 \textit{Lpar1} gene (Tsujii et al., 2009). Taken together, these results suggest that LPA signaling via mutated LPA1 is mainly involved in the pathogenesis of rat lung and liver tumors (Table 2).

\textbf{Pattern and location of mutations}

\textbf{Pattern of mutations.} In DLD1 and SW48 cells, three

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

<table>
<thead>
<tr>
<th>Receptors</th>
<th>Cells</th>
<th>Mutation patterns</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPA1</td>
<td>MG62</td>
<td>314 CGC to CGT (Arg to Arg)</td>
<td>Okabe et al., 2010a</td>
</tr>
<tr>
<td>LPA2</td>
<td>DLD1</td>
<td>136 GTG to GTA (Val to Val), 146 CGC to CAC (Arg to His)</td>
<td>Tsujino et al., 2010</td>
</tr>
<tr>
<td></td>
<td>SW48</td>
<td>136 GTG to GTA (Val to Val), 230 CCC to CTC (Pro to Leu)</td>
<td>Tsujino et al., 2010</td>
</tr>
<tr>
<td>LPA3</td>
<td>MG63</td>
<td>247 GCG to GTG (Ala to Val)</td>
<td>Okabe et al., 2010a</td>
</tr>
<tr>
<td>LPA4</td>
<td>DLD1</td>
<td>232GCG to CAC (Arg to His)</td>
<td>Tsujino et al., 2010</td>
</tr>
</tbody>
</table>

---

**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 CDA 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.

<table>
<thead>
<tr>
<th>Receptors</th>
<th>Tissues</th>
<th>Species</th>
<th>Incidence (%)</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPA₁</td>
<td>Lung adenomas</td>
<td>rat</td>
<td>2/12 (16.7)</td>
<td>Yamada et al., 2009</td>
</tr>
<tr>
<td></td>
<td>Lung adenocarcinomas</td>
<td>rat</td>
<td>7/17 (41.2)</td>
<td>Yamada et al., 2009</td>
</tr>
<tr>
<td></td>
<td>HCCs</td>
<td>rat</td>
<td>12/27 (44.4)</td>
<td>Obo et al., 2009</td>
</tr>
<tr>
<td>LPA₃</td>
<td>Lung adenocarcinomas</td>
<td>rat</td>
<td>N.D.</td>
<td>Wakabayashi et al., 2010</td>
</tr>
<tr>
<td>LPA₅</td>
<td>Lung adenocarcinomas</td>
<td>rat</td>
<td>N.D.</td>
<td>Wakabayashi et al., 2010</td>
</tr>
<tr>
<td>LPA₅</td>
<td>Lung adenocarcinomas</td>
<td>rat</td>
<td>N.D.</td>
<td>Wakabayashi et al., 2010</td>
</tr>
<tr>
<td>LPA₅</td>
<td>HCCs</td>
<td>rat</td>
<td>N.D.</td>
<td>Obo et al., 2009</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Cells</th>
<th>LPA receptors</th>
<th>LPA₁</th>
<th>LPA₂</th>
<th>LPA₃</th>
<th>LPA₅</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLD1</td>
<td>unmethylated</td>
<td>unmethylated</td>
<td>highly methylated</td>
<td>highly methylated</td>
<td>moderately methylated</td>
</tr>
<tr>
<td>SW48</td>
<td>unmethylated</td>
<td>unmethylated</td>
<td>highly methylated</td>
<td>highly methylated</td>
<td>moderately methylated</td>
</tr>
<tr>
<td>HTC116</td>
<td>unmethylated</td>
<td>unmethylated</td>
<td>unmethylated</td>
<td>weakly methylated</td>
<td>weakly methylated</td>
</tr>
<tr>
<td>SW480</td>
<td>unmethylated</td>
<td>unmethylated</td>
<td>moderately methylated</td>
<td>highly methylated</td>
<td>highly methylated</td>
</tr>
<tr>
<td>CaCo2</td>
<td>unmethylated</td>
<td>unmethylated</td>
<td>moderately methylated</td>
<td>highly methylated</td>
<td>moderately methylated</td>
</tr>
<tr>
<td>LoVo</td>
<td>unmethylated</td>
<td>unmethylated</td>
<td>moderately methylated</td>
<td>highly methylated</td>
<td>moderately methylated</td>
</tr>
</tbody>
</table>

Tsujino et al., 2010.

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

<table>
<thead>
<tr>
<th>Cells</th>
<th>Species</th>
<th>LPA receptors</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>LL/2</td>
<td>mouse</td>
<td>unmethylated</td>
<td>highly methylated</td>
</tr>
<tr>
<td>B16F0</td>
<td>mouse</td>
<td>highly methylated</td>
<td>highly methylated</td>
</tr>
<tr>
<td>FM3A</td>
<td>mouse</td>
<td>highly methylated</td>
<td>highly methylated</td>
</tr>
<tr>
<td>L1210</td>
<td>mouse</td>
<td>highly methylated</td>
<td>highly methylated</td>
</tr>
<tr>
<td>RH7777</td>
<td>rat</td>
<td>highly methylated</td>
<td>highly methylated</td>
</tr>
<tr>
<td>B103</td>
<td>rat</td>
<td>highly methylated</td>
<td>highly methylated</td>
</tr>
<tr>
<td>COS</td>
<td>rat</td>
<td>highly methylated</td>
<td>moderately methylated</td>
</tr>
<tr>
<td>RLCNR</td>
<td>rat</td>
<td>unmethylated</td>
<td>highly methylated</td>
</tr>
<tr>
<td>C6</td>
<td>rat</td>
<td>N.E.</td>
<td>highly methylated</td>
</tr>
<tr>
<td>MFH</td>
<td>rat</td>
<td>unmethylated</td>
<td>highly methylated</td>
</tr>
</tbody>
</table>

N.E.: not examined.
Lysophosphatidic acid receptors and cancer

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 CDA diet (Obo et al., 2009; Yamada et al., 2009). The biological significance of mutations in codon 295 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 LPA1 (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 LPA1 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 (Tsujiiuchi 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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