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Bioactive lysolipids in cancer and angiogenesis

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Abstract

While normal angiogenesis is critical for development and tissue growth, pathological angiogenesis is important for the growth and spread of cancers by supplying nutrients and oxygen as well as providing a conduit for distant metastasis. The interaction among extracellular matrix molecules, tumor cells, endothelial cells, fibroblasts, and immune cells is critical in pathological angiogenesis, in which various angiogenic growth factors, chemokines, and lipid mediators produced from these cells as well as hypoxic microenvironment promote angiogenesis by regulating expression and/or activity of various related genes. Sphingosine 1-phosphate and lysophosphatidic acid, bioactive lipid mediators which act via specific G protein-coupled receptors, play critical roles in angiogenesis. In addition, other lipid mediators including prostaglandin E_2, lipoxin, and resolvins are produced in a stimulus-dependent manner and have pro- or anti-angiogenic effects, presumably through their specific GPCRs. Dysregulated lipid mediator signaling pathways are observed in the contxt of some tumors. This review will focus on LPA and S1P, two bioactive lipid mediators in their regulation of angiogenesis and cell migration that are critical for tumor growth and spread.

Keywords

Sphingosine 1-phosphate; Lipid mediator; Cancer; Migration; Angiogenesis

1. Introduction

Lipids, important constituents of the diet, serve as energy source and major structural components of biological membranes. In addition to these fundamental roles, many lipids such as lysophospholipids and fatty acids have been proposed to function as signaling molecules in intercellular and intracellular locales (Rosen & Goetzl, 2005; Shimizu, 2009; Xie, Gibbs, & Meier, 2002). Lipid mediators that function as extra-cellular signaling molecules are synthesized by specific enzymes in both intracellular and extracellular milieu while intracellularly produced lipid mediators are released via exocytosis or transporter-mediated pathways (Nakanaga, Hama, & Aoki, 2010; Nishi, Kobayashi, Hisano, Kawahara, & Yamaguchi, 2014). Subsequently, binding to specific receptors activates downstream signaling cascades in target cells. A single lipid mediator can act as an agonist for multiple

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Conflict of interest

The authors declare that there are no conflicts of interest.

receptor subtypes, and the expression patterns in these receptor subtypes enable different cellular responses such as migration, proliferation, apoptosis, cell survival and differentiation.

Numerous knockout mice in which lipid receptors and metabolizing enzymes have been deleted were generated and analysis of these mice revealed the involvement of such mediators in a wide range of physiological phenomena including inflammation, immunity, and angiogenesis. For example, during embryonic development, precisely-controlled vascular network formation is regulated by key pro- and anti-angiogenic factors including vascular endothelial growth factor (VEGF) and lipid mediators. While angiogenesis does not occur frequently under homeostatic conditions in the postnatal period, angiogenesis is critical for cancer progression. Uncontrolled angiogenesis enables tumor growth by supplying oxygen and nutrients to the rapidly growing tumor and allowing metastasis to distant sites. This review will focus on the bioactive lipid mediators that regulate angiogenesis and cell migration.

2. Sphingosine 1-phosphate signaling

Sphingosine 1-phosphate (S1P), a bioactive lipid mediator that occurs abundantly in plasma, regulates many physiological processes including angiogenesis, vascular permeability, inflammation, and immunity (Brinkmann, 2007; Proia & Hla, 2015). Intracellularly produced S1P was proposed to function as a second messenger, as well as a ligand for its specific G-protein coupled receptors expressing on target cell surface after secreted from the cells via its specific transporters such as SPNS2 (Hisano, Nishi, & Kawahara, 2012). In our opinion, intracellular S1P plays a role as a metabolic intermediate in interconnected lipid metabolic pathways (Hla & Dannenberg, 2012; Nakahara et al., 2012). Its function as a *bona fide* second messenger has been questioned since physiological and genetic evidence to support this mode of action are lacking.

Since the first S1P receptor was cloned from human endothelial cells as an orphan receptor (Hla & Maciag, 1990), numerous studies have revealed the mechanism of S1P signaling and its biological actions (Gonzalez-Cabrera, Brown, Studer, & Rosen, 2014; Takuwa et al., 2001). So far, five S1P receptors (S1PR1–5) have been identified in mammals and characterized. S1PR1, S1PR2, and S1PR3 are ubiquitously expressed on various cell types, including those of the immune, cardiovascular, and central nervous systems, whereas S1PR4 and S1PR5 show more restricted expression patterns in the lymphoid tissues, lung and central nervous systems, respectively (Chae, Proia, & Hla, 2004; Graler, Bernhardt, & Lipp, 1998; Ishii et al., 2001; Terai et al., 2003; Yamaguchi et al., 2003). Genetic studies with transgenic mice as well as pharmacological studies have revealed the physiological roles of each S1P receptor subtype. Genetic deletion of *S1pr1* in mice leads to embryonic lethality due to severe edema and hemorrhage, and deletion of three receptors, namely *S1pr1*, *S1pr2*, and *S1pr3* results in a more severe hemorrhagic phenotype at an earlier stage, indicating these S1P receptor subtypes cooperatively regulate vascular development (Kono et al., 2004; Liu et al., 2000). In addition, the clinically important role of S1PR1 as a regulator of lymphocyte circulation was uncovered since the discovery of fingolimod (FTY720), an analogue of sphingosine, which is now an approved oral drug for multiple sclerosis (Cyster

& Schwab, 2012). Its phosphorylated form can be recognized by S1P receptors except for S1PR2, and induces receptor internalization and degradation. Therefore, this drug is classified as a functional antagonist. FTY720 functions as an immunomodulatory agent by suppressing lymphocyte egress from lymphoid tissues and reducing the number of circulating lymphocytes.

At the cellular level, S1P signaling regulates fundamental functions including cell growth, apoptosis, and cell migration, which are also involved in many diseases including inflammatory diseases and cancer progression (Kihara, Mitsutake, Mizutani, & Igarashi, 2007; Yester, Tizazu, Harikumar, & Kordula, 2011). Indeed, it has been reported that the expression of some S1P receptor subtypes and S1P-producing enzymes are dysregulated in cancer tissues (Watson et al., 2010; Zhang et al., 2014). It has been considered that the S1P signaling plays a key role in multiple processes in cancer progression such as cell growth, invasion, metastasis, and angiogenesis.

3. Cell migration, invasion, and metastasis

Cell migration is a fundamental phenomenon that occurs in many biological processes including embryogenesis, inflammatory responses, wound healing, lymphatic egress, and cancer progression. A dynamic reorganization of the actin cytoskeleton is essential for cell migration and regulated by chemoattractants mainly through Rho and Rac GTPase subfamilies. Rho regulates stress fiber formation and focal adhesions while Rac induces lamellipodia formation by promoting peripheral actin assembly at the leading edge of migrating cells (Ridley, 2015).

S1P signaling through S1PR1, S1PR2, and S1PR3 is known to be involved in cell migration by regulating Rho/Rac pathways. Each S1P receptor subtype associates with different heterotrimeric G protein α subunits. S1PR1 couples mostly with G_i, whereas S1PR2 and S1PR3 can associate with G_i, $G_{12/13}$, and G_q. However, S1PR2 and S1PR3 show preferential coupling to $G_{12/13}$, and G_q, respectively. The activation of S1PR1 and S1PR3 induces cell migration via G_i or $G_{12/13}$-dependent Rho and Rac activation (Arikawa et al., 2003; Paik, Chae, Lee, Thangada, & Hla, 2001). In contrast to S1PR1 and S1PR3, S1PR2 signaling negatively regulates cell motility although this mechanism still remains unclear. S1P-induced inhibition of Rac and migration were observed in S1PR2-overexpressing CHO cells and B16 melanoma cells, in which Rho activation was required for the inhibitory effect (Arikawa et al., 2003; Okamoto et al., 2000). In addition, PTEN, a lipid phosphatase, has been reported to act downstream of the Rho and be necessary for S1PR2-mediated inhibition of migration in mouse embryonic fibroblasts (Sanchez et al., 2005), while another study shows that S1PR2-mediated activation of $G_{12/13}$ and Rho also inhibits cell migration in PTEN-null GNS-3314 glioblastoma cells (Malchinkhuu et al., 2008). Furthermore, S1P stimulation does not induce Rac suppression in U118 glioblastoma cells exogenously overexpressing S1PR2, in which cell migration is inhibited (Lepley, Paik, Hla, & Ferrer, 2005). In murine macrophages, S1PR2-inhibition of migration is independent of PTEN but requires cAMP/PKA signaling (Michaud, Im, & Hla, 2010). These studies suggest that the S1PR2-mediated inhibition of cell migration can be regulated by multiple mechanisms.

Migratory response against S1P is dependent on the expression of S1P receptor subtypes. S1P stimulation induces cell migration of endothelial cells, immune cells, astrocytes, and osteoclasts (Ishii et al., 2009; Kimura et al., 2000; Malchinkhuu et al., 2005; Matloubian et al., 2004), whereas endothelial migration is suppressed by S1PR2 overexpression (Ryu et al., 2002). The anti-migratory effect is observed in cells that express S1PR2 predominantly such as vascular smooth muscle and mast cells when exposed to S1P. On the other hand, JTE013, an inhibitor of S1PR2, abolished the inhibition of cell migration (Takashima et al., 2008; Yokoo et al., 2004). Furthermore, among various human gastric cancer cell lines, MKN1 and HGC-27 cells, which express high S1PR3, show the S1P dependent activation of cell migration, while AZ-521 and MK74 cells, which are expressing higher S1PR2 than S1PR3, exhibit anti-migratory effect (Yamashita et al., 2006). As for other cancer cell lines, there are numerous *in vitro* studies that describe S1P inhibition of cell migration in melanoma, osteosarcoma, and breast cancer cells (Sadahira, Ruan, Hakomori, & Igarashi, 1992; Spiegel et al., 1994), while S1P-induced cell migration is observed in pancreatic, esophageal, prostate, and ovarian cancer cells (Alfranca et al., 2008; Miller, Alvarez, Spiegel, & Lebman, 2008; Pai et al., 2001a, 2001b; Park et al., 2007).

In addition to motility, degradation of extracellular matrix by secreted proteases is an important factor for cancer invasion and metastasis. Plasminogen activator system is an enzymatic cascade for this degradation process. Plasminogen activators extracellularly convert inactive plasminogen to plasmin, a serine protease, which directly degrades various extracellular matrix molecules including fibronectin, laminin, vitronectin, proteoglycans, and fibrin, as well as activates matrix metalloproteinases (MMPs). S1P signaling through its receptors has been shown to upregulate the expression of components of plasminogen activator system and MMP2/9 (Bryan et al., 2008; Devine, Smicun, Hope, & Fishman, 2008; Young, Pearl, & Van Brocklyn, 2009). Furthermore, the expression of matriptase, another serine protease, was induced by S1P signaling probably through S1PR2 and/or S1PR3 (Benaud et al., 2002). Especially in glioblastoma cells, the S1PR2 inhibitor or siRNA treatment abolished the S1P-induced upregulation of plasminogen activator system (Bryan et al., 2008), suggesting the contribution of S1PR2 to cancer invasion and metastasis although S1PR2 generally shows inhibitory effect in cell migration as mention above. Taken together, the S1P signaling through receptors is thought to regulate caner invasion and metastasis by regulating cell migration and degradation of extracellular matrix proteins through complex mechanisms.

Recently, the involvement of SPNS2, an S1P transporter, in cell migration has been proposed. SPNS2, identified by genetic analysis of a cardia bifida zebrafish mutant, exports S1P from vascular and lymphatic endothelial cells (Hisano, Kobayashi, Yamaguchi, & Nishi, 2012; Kawahara et al., 2009). A recent study examined the role of S1P secretion in hepatocyte growth factor (HGF)-induced angiogenesis. HGF promotes endothelial cell migration through lamellipodia formation, barrier function, and tumor formation. HGF-induced migration and lamellipodia formation are attenuated by treatment of *SPNS2*, *SPHK1*, or *S1PR1* siRNA, and SPNS2 can associate with S1PR1 and SPHK1 by HGF stimulation in lung endothelial cells, suggesting that autocrine pathway of the S1P signaling can regulate cell migration (Fu et al., 2016). On the other hand, *SPNS2* siRNA treatment conversely promotes cell migration in lung cancer cell lines (Bradley et al., 2014). In these

cells, *SPNS2* knockdown causes accumulation of intracellular S1P as well as activation of PI3K/Akt and Jak/Stat3 pathway, which are crucial for cell migration. Indeed, *SPNS2* mRNA level is significantly reduced in lung cancer tissues from patients with stage 2B and stage 3 disease compared with the adjacent normal tissues, indicating downregulation of SPNS2 is a potential risk factor for lung cancer (Bradley et al., 2014). The mechanism by which SPNS2 negatively regulates cell migration in these cell lines remains unclear and further studies are required for developing this concept for potential therapeutic strategy for cancer metastasis. In this context, *Spns2* was recently identified as a major metastatic regulatory gene from an unbiased screen for mouse melanoma spread to the lung. The authors suggested that SPNS2 acts via immunological mechanisms to promote antitumor immunity (van der Weyden et al., 2017).

4. Sphingosine 1-phosphate and angiogenesis

Angiogenesis performs a critical role in the growth and spread of cancers by enhancing nutrients and oxygen supply as well as providing a conduit for distant metastasis. Pathological angiogenic process is regulated by the tumor microenvironment comprised of extracellular matrix molecules, tumor cells, endothelial cells, fibroblasts, and immune cells. These cells can interact each other using signaling molecules thus promoting angiogenesis and metastasis (Martin, Fukumura, Duda, Boucher, & Jain, 2016). Numerous studies have been carried out to show the involvement of S1P signaling in vascular development. Pioneering studies from the Proia laboratory showed that *S1pr1* knockout mice are embryonic lethal because of vascular defect and severe hemorrhage (Liu et al., 2000). Among five S1P receptors, S1PR1/2/3 expression is detected in endothelial cells (Lee et al., 1999). S1PR2 and S1PR3 are also involved in vascular development because *S1pr1/2/3* triple knockout mice exhibit earlier and more severe hemorrhage although single depletion of S1PR2 or S1PR3 does not cause any vascular developmental defects (Ishii et al., 2002; Kono et al., 2004). Furthermore, analyses of endothelial specific *S1pr1* knockout mice have revealed that endothelial S1PR1 plays a key role in maintaining vascular stability by suppressing excessive sprouting and promoting barrier function (Ben Shoham et al., 2012; Gaengel et al., 2012; Jung et al., 2012). The endothelial hypersprouting phenotype is also observed in S1PR1-knockdown zebrafish by morpholino oligonucleotides, but not in genetic knockout zebrafish (Ben Shoham et al., 2012; Gaengel et al., 2012; Hisano et al., 2015; Mendelson, Zygmunt, Torres-Vazquez, Evans, & Hla, 2013). Interestingly, in addition to S1P in the blood, fluid shear stress, which occurs due to blood flow, can activate endothelial S1PR1, which increases adherens junction stability and promotes vascular barrier function (Jung et al., 2012).

VEGF is one of most prominent angiogenic growth factors, and regulates both angiogenesis and vasculogenesis by binding to tyrosine kinase receptors, VEGFRs. In contrast to the hypersprouting phenotype of *S1pr1* deletion, inducible *Vegfr2* deletion in endothelial cells causes strongly reduced endothelial sprouting and vessel density (Gavard & Gutkind, 2006). Vascular endothelial (VE)-cadherin is a major determinant of permeability of the endothelium, composing adherens junctions, the loss of which causes retinal hypersprouting phenotype similar to *S1pr1* knockout mice (Gaengel et al., 2012). While the S1PR1 activation induces stabilization of VE-cadherin localization at endothelial junctions (Lee et

al., 1999), the VEGF signal promotes VE-cadherin destabilization at endothelial junctions and triggers its subsequent internalization (Gavard & Gutkind, 2006). Indeed, VEGF was initially discovered by Dvorak and co-workers as vascular permeability factor (VPF) (Senger et al., 1983). These studies propose a functional antagonism between S1PR1 and VEGFR2 signaling, which regulates the VE-cadherin localization and endothelial junctional stability. VEGFR2 signaling plays a critical role at the early process of the angiogenic program followed by S1PR1 signaling stimulates stabilization of newly formed vasculature at the later phase. This mechanism may be a critical in the formation of a primary vascular network.

S1PR1 expression level is induced in the vasculature upon the implantation of tumor cells, and its suppression by siRNA reduces tumor angiogenesis and vascular maturation, resulting in less primary tumor growth (Chae, Paik, Furneaux, & Hla, 2004). Furthermore, repeated administration of anti-S1P antibody inhibits proangiogenic effect of VEGF *in vivo* and tumor progression in multiple murine models (Visentin et al., 2006). These studies suggest that the S1P signaling plays a proangiogenic role in tumors, but S1PR1 is expressed in almost cell types including endothelial, stromal and cancer cells, which are likely inhibited by *S1pr1*-siRNA and anti-S1P antibody. Thus, the function of endothelial S1PR1 for the pathological angiogenic process remains to be further defined.

Interleukin-8 (IL-8), a chemokine produced from various cell types (macrophages, vascular smooth muscle cells (VSMCs), and endothelial cells), activates CXCR1 receptors on endothelial cells to promote an angiogenic response (Li et al., 2005; Li, Dubey, Varney, Dave, & Singh, 2003). IL-8 is upregulated in various cancers including breast, pancreatic, prostate, gastric, bladder, ovarian, lung, and melanoma. In addition, a positive correlation between ectopic IL-8 expression and poor prognosis exists for ovarian, pancreatic, and lung cancers (Chen et al., 2003; Chen, Chen, Chou, & Lin, 2012; Li et al., 2003). Furthermore, S1P stimulation promotes the IL-8 signaling by upregulating its expression and release of this chemokine from ovarian and breast cancer cell lines *in vitro* (Boucharaba et al., 2009; Schwartz et al., 2001). The studies using specific inhibitors in epithelial cells show that the expression and secretion of IL-8 are regulated independently; the S1PR1 signaling induces IL-8 expression while the S1PR2 signaling via NF-κB and Rac1 might regulate IL-8 secretion from cells (Brunnert, Piccenini, Ehrhardt, Zygmunt, & Goyal, 2015; O'Sullivan, Hirota, & Martin, 2014).

Moreover, angiogenesis is induced by hypoxia, which is commonly seen in rapidly growing tumors. Hypoxia-induced angiogenesis is predominantly mediated by the hypoxia-inducible factors (HIFs), which are oxygen-dependent transcriptional activators. Hypoxia induces SPHK1 expression via HIF-2α, which directly binds the *SPHK1* promoter region in glioma cells, resulting in increased S1P release to the medium (Anelli, Gault, Cheng, & Obeid, 2008). Adenocarcinoma cells show hypoxia dependent induction of SPHK2 expression and S1P release (Schnitzer, Weigert, Zhou, & Brune, 2009). Although S1P release mechanism from these cancer cells remains unknown, S1P transporters likely function in these cancer cells because even when SPHKs are overexpressed, S1P transporters are needed to release S1P (Hisano, Kobayashi, Kawahara, Yamaguchi, & Nishi, 2011). Recently, it has been reported that SPHK1 expression is upregulated in 786–0 renal cancer cells, which is

abolished by *HIF-2α* siRNA treatment, suggesting HIF-2α is an upstream regulator of SPHK1 as shown in glioma cells (Salama et al., 2015), while another study using different renal cancer cells (CAKI-1 and A498) showed that hypoxia-induced HIF-2α upregulation is abolished by *SPHK1, SPNS2*, or *S1PR1* siRNA treatment, suggesting that SPHK1/SPNS2/S1PR1 signaling axis acts as a regulator of HIF-2α expression (Watson et al., 2010). Further, S1PR2-signaling is also reported to positively regulate HIF-1α expression by increasing the protein stability (Michaud, Robitaille, Gratton, & Richard, 2009). Taken together, the S1P signaling via S1PR1 and/or S1PR2 might be potential targets to suppress hypoxia-induced angiogenesis. In addition, about 65% of plasma S1P is associated with HDL (high density lipoprotein) which contains several lipoproteins and various lipids including sterols, triglycerides, vitamins, and sphingolipids. As reviewed by Tan et al. (Tan, Ng, & Bursill, 2015), serum HDL level is elevated in physiological ischemia and HDL plays a role in hypoxia-driven angiogenesis by regulating HIF-1α expression via SR-BI, HDL receptor (Tan et al., 2014). HDL containing S1P also activates S1PR1 on endothelial cells and its downstream signaling pathways (Galvani et al., 2015; Sato & Okajima, 2010; Swendeman et al., 2017), suggesting that S1PR1 and SR-BI cooperatively regulate hypoxia-induced angiogenesis.

5. Lysophosphatidic acid and angiogenesis

Similar to S1P, lysophosphatidic acid (LPA) is a bioactive lysophospholipid, regulating proliferation, migration, and survival of many cell types through its specific GPCRs. Based on primary sequence similarity, LPA receptors are classified into two subfamilies, endothelial differentiation gene (Edg) family and non-Edg (P2Y) family. LPAR1/2/3 comprise the Edg family with five S1P receptors, and other LPA receptors (LPAR4/5/6, GPR87, and P2Y10) are classified into non-Edg (P2Y) family.

LPA exists in plasma as a circulatory lipid mediator. The secreted lysophospholipase D enzyme called autotaxin (ATX), encoded by the *Enpp2* gene, is mainly responsible for LPA production from lysophosphatidylcholine. In heterozygous *Enpp2*$^{+/-}$ mice, which do not show obvious abnormal phenotypes, protein expression and enzymatic activity of ATX in plasma is about half of wild-type mice as well as the plasma LPA level is also reduced to half of wild-type mice (Tanaka et al., 2006; van Meeteren et al., 2006). Homozygous *Enpp2*$^{-/-}$ mice die at embryonic day 9.5–10.5 due to severe vascular phenotype in the yolk sac and embryos, as well as neural tube defects (Koike et al., 2011; Tanaka et al., 2006; van Meeteren et al., 2006). In zebrafish, *enpp2*-knockdown causes developmental vascular defects (Yukiura et al., 2011). Furthermore, transgenic mice overexpressing ATX also exhibit severe vascular defects causing embryonic lethality at embryonic day 9.5 (Yukiura, Kano, Kise, Inoue, & Aoki, 2015a). Taken together, ATX-derived LPA plays an essential role in angiogenesis and need to be strictly regulated. In zebrafish, single LPA receptor knockdown by morpholino oligonucleotides do not cause vascular defects, while *lpar1* and *lpar4* double knockdown embryos exhibit similar vascular defects as *enpp2*-knockdown (Yukiura et al., 2011). On the other hand, some of *Lpar4* knockout mice are embryonic lethal due to hemorrhages and edema although their phenotypes are not as severe as *Enpp2* knockout mice (Sumida et al., 2010). These studies suggest that ATX is an indispensable factor and LPAR4 plays a key role in angiogenesis in cooperation with other LPA receptors.

LPA treatment of various cancer cell lines promotes the expression and release of IL-8, which is a potent angiogenic factor as mentioned above (Boucharaba et al., 2009; Chen, Chen, et al., 2012; Schwartz et al., 2001; Shida et al., 2003). Ovarian and cervical cancer cells express LPAR1/2/3, and knockdown of *LPAR2* and/or *LPAR3* results in abolishment of LPA-induced IL-8 production while *LPAR1* knockdown did not result in a similar effect (Chen, Chen, et al., 2012; Yu et al., 2008). Indeed, when cervical cancer cells with different LPA receptor expression patterns are injected into mice to assess tumorigenicity, the microvessel density and tumor size are suppressed in the *LPAR2/3* double knockdown cells, which is as low as the *LPAR1/2/3* triple knockdown cells (Chen, Chen, et al., 2012). The promoter region for *IL-8* harbors AP-1 and NF-κB transcription factor-binding sites. Both of these transcription factors synergistically activate the LPA-dependent IL-8 expression in ovarian cancer cells, while only NF-κB transcription factor is involved in cervical cancer cells (Chen, Chen, et al., 2012; Fang et al., 2004). Among colon cancer cell lines, LPAR1 activation induces IL-8 release from DLD1 cells, while other colon cancer cells (HT29 and WiDR) predominantly expressing *LPAR2* but not *LPAR1* also have an ability to release IL-8 (Shida et al., 2003). Even in normal cell lines including endometrial stromal cells, placental trophoblasts, and chondrocytes, the LPA signaling through some of LPA receptors induces IL-8 production in a NF-κB-dependent manner (Chen et al., 2008, 2010; Chuang et al., 2014). Taken together, angiogenesis mediated by IL-8 in both normal and cancer cells may be regulated by the activation of LPA signaling in which several LPA receptor subtypes are involved in a cell-type-specific manner.

Extracellular S1P and LPA are converted to sphingosine and monoacylglycerol, respectively by dephosphorylation at the cell surface via LPPs (lipid phosphate phosphatases), membrane proteins, which interrupts the activation of S1P or LPA receptors. Endothelial-specific *Lpp3* knockout mice also exhibit lethal vascular leakage and hemorrhage (Chatterjee, Baruah, Lurie, & Wary, 2016; Panchatcharam et al., 2014) as observed in *S1pr1* knockout, *Enpp2* knockout, and *Enpp2* overex-pressing mice. The vascular barrier defect caused by LPP3 deficiency seems to be associated with LPA receptor signaling, because the LPARs antagonist administration into *Enpp2* knockout mice attenuated endothelial barrier defect (Panchatcharam et al., 2014). *In vitro* experiment assessing the monolayer cell barrier function showed not S1P signaling but LPA signaling decreases the endothelial barrier function (Ren et al., 2013; Singleton, Dudek, Chiang, & Garcia, 2005). Furthermore, it has been reported that LPP3 localizes in specific cell–cell contact sites where LPAR6 signaling is activated and suppresses its signaling (Yukiura, Kano, Kise, Inoue, & Aoki, 2015b). The *Lpp3* deficiency in endothelial cells does not affect blood LPA level but disrupts barrier function (Panchatcharam et al., 2014). Taken together, LPP3 might localize closely with LPA receptors and regulate the LPA amount in some specific space that would be recognized by LPA receptors. Additionally, several tumors are highly expressing LPP3, and the inhibitory antibody against LPP3 suppresses bFGF and VEGF induced capillary formation and tumor growth (Chatterjee, Humtsoe, Kohler, Sorio, & Wary, 2011; Wary & Humtsoe, 2005), suggesting LPP3 as a potential therapeutic target.

6. Prostaglanoid signaling and angiogenesis

Prostaglandin E_2 (PGE_2) is known as another proangiogenic lipid mediator. Three distinct PGE synthases generate PGE_2 from PGH_2, which is also a precursor for other prostanoids including PGI_2, PGF_2, PGD_2, and thromboxane A_2 (TXA_2). The cyclooxygenase (COX) enzymes contribute to PGH_2 production from arachidonic acid, which is derived from membrane phospholipids. Intracellularly produced PGE_2 is secreted by its specific transporter (PGT/OATP2A1/SLCO2A1) (Chan, Satriano, Pucci, & Schuster, 1998), which allow autocrine and/or paracrine signaling via four GPCRs which are named EP (E-type prostanoid) receptors (EP1–4).

COX-1 encoded by the *Ptgs1* gene is constitutively and ubiquitously expressed while COX-2 encoded by the *Ptgs2* gene is an inducible iso-form by various stimulations such as inflammation and pathological conditions (Hla & Neilson, 1992). Indeed, basal level of PGE_2 is mostly diminished in *Ptgs1* knockout mice, while lipopolysaccharide (LPS)-induced PGE_2 synthesis is not observed in *Ptgs2* knockout mice and elevated expression of COX-2 leads to an increase in PGE_2 level in the isolated peritoneal macrophages (Brock, McNish, & Peters-Golden, 1999; Langenbach et al., 1995; Morham et al., 1995). *Ptgs1* or *Ptgs2* single knockout mice can be grown to adulthood with some phenotypes such as parturition problems, peritonitis, kidney malfunction, and female infertility (Langenbach, Loftin, Lee, & Tiano, 1999; Lim et al., 1997; Morham et al., 1995). Angiogenic defects during development are not observed even in *Ptgs1* and *Ptgs2* double knockout mice although they die in the postnatal period because of premature closure of the ductus arteriosus (Loftin et al., 2001; Reese et al., 2000), suggesting prostaglandins generated by COX-1/2 are not essential for developmental angiogenesis. Meanwhile, a large number of studies suggest that PGE_2 generated by COX-2 is a key factor promoting tumor-associated angiogenesis. COX-2 expression is upregulated in neovasculature cells of various tumor including the lung, colon, prostate, and breast (Masferrer et al., 2000; Soslow et al., 2000). When the lung carcinoma cells are engrafted into mice, the tumor growth and vascular density are decreased in *Ptgs2* knockout mice and COX-2 inhibitor-treated mice, but not in *Ptgs1* knockout mice (Amano et al., 2009; Williams, Tsujii, Reese, Dey, & DuBois, 2000). In addition, overexpression of human *PTGS2* gene in the mammary glands of transgenic mice results in the formation of mammary adenocarcinoma in multiparous mice which are completely inhibited by NSAIDs and COXIBs. These data suggest that prostaglandins secreted from the COX-2 pathway cooperate with other mechanisms to promote tumor development. In addition, the induction of angiogenic switch by PGE_2 receptor EP2 appears to be important in this model (Chang, Ai, Breyer, Lane, & Hla, 2005; Chang et al., 2004; Chang, Liu, Wu, & Hla, 2005; Liu et al., 2001). The gene deletion for EP3 also suppresses tumor growth and angiogenesis (Amano et al., 2003; Amano et al., 2009). The *Ptgs2* gene deletion in the model mice of familial adenomatous polyposis dramatically reduces the polyp growth and vascular density (Oshima et al., 1996; Seno et al., 2002). The resemble phenotypes are observed in the mice deleting the gene encoding EP2 but not EP1 and EP3 receptors in this model mice (Seno et al., 2002; Sonoshita et al., 2001). Furthermore, there is a report that the selective agonist for EP4 receptor promotes angiogenesis *in vivo* (Rao et al., 2007), presenting that the COX-2/PGE_2

signaling pathway via EP receptors plays a critical role in promoting tumor-associated angiogenesis.

As mechanisms of COX-2/PGE_2-mediated angiogenesis, VEGF production is increased in response to COX-2 and/or PGE_2 in various cell types, and this induction is attenuated by the treatment of inhibitors for COX-2 or PGE synthase (Eibl et al., 2003; Finetti et al., 2012; Miura et al., 2004; Murono et al., 2001; Pai et al., 2001a, 2001b). In addition, the COX-2 expression is also stimulated by VEGF (Hernández et al., 2001; Wu et al., 2006), indicating the positive feedback loop between COX-2/PGE_2 and VEGF pathway to amplify these angiogenic effects.On the other hand, the VEGF-independent pathway in COX-2/PGE_2-mediated angiogenesis has been proposed in colon tumors, which are resistant to VEGFR2 inhibitors (Fischer et al., 2007; Xu et al., 2014). Both the COX-2 inhibitor and COX-2 overexpression do not affect the VEGF production and VEGFR2 activation, as well as VEGFR2 inhibitory antibodies cannot block COX-2-induced angiogenesis. Taken together, simultaneous blocking both pathways might be an effective therapy in tumors where angiogenesis are promoted by VEGF and COX-2/PGE_2 independently (Xu & Croix, 2014).

7. Anti-angiogenic lipid mediators

In contrast to proangiogenic mediators mentioned above, several lipid mediators are reported to have anti-angiogenic effects. Lipoxin A4 (LXA4), one of arachidonic acid metabolites, can be a ligand for a GPCR called ALXR/FPRL-1 (Fiore, Maddox, Perez, & Serhan, 1994). LXA4 treatment reduces the production of proangiogenic factors such as PGE_2, IL-8, and VEGF *in vitro* and *in vivo* (Jin et al., 2009; Marginean & Sharma-Walia, 2015; Xu, Zhao, Lin, Chen, & Huang, 2012). In addition, LXA downregulates the VEGFR2 signaling by dephosphorylating the tyrosine residues of VEGFR2 and translocating from lipid raft which facilitates efficient signal transduction by recruiting multiple signaling complexes in close proximity (Baker, O'Meara, Scannell, Maderna, & Godson, 2009; Marginean & Sharma-Walia, 2015). Furthermore, ALXR stimulation with a LXA4 analog suppresses VEGF-promoted corneal angiogenesis (Jin et al., 2009).

Resolvin D1 (RvD1) and E1 (RvE1) produced from docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), respectively, also have an anti-angiogenic activity *in vivo*. Treatment with these lipid mediators suppresses corneal and retinal angiogenesis in pathological lesion (Connor et al., 2007; Rajasagi et al., 2011). Dietary intake of DHA and EPA can suppress retinal angiogenesis probably due to their metabolites, RvD1 and RvE1 without alteration in the VEGF level (Connor et al., 2007), while topical subconjunctival injection causes VEGF transcriptional reduction (Jin et al., 2009). Thus, an involvement of VEGF in these pathways is still unclear, and further analysis is awaited.

8. Concluding remarks

Receptors expressed on cell surface are the most readily targeted in current pharmacologic strategies. In fact, FTY720, an S1P analogue, has been approved as oral therapy for multiple sclerosis, and many compounds targeting lipid mediator receptors are under development as potential new medicine. On the other hand, upstream molecules in signaling pathways such

as metabolizing enzymes and transporters have been also reported as important factors in several cancers (Bradley et al., 2014; Umezu-Goto et al., 2004; van der Weyden et al., 2017), although targeting these upstream molecules would affect additional pathways that act through multiple receptors. A lipid mediator can be a ligand for multiple receptors, enabling diverse and complex cellular responses in different cell types. Furthermore, in the case of GPCRs, because each receptor can associate with multiple heterotrimeric G protein α subunits and has differential affinities, activation of same receptor may result in different cellular responses. In addition, many of lipid mediator receptors described above are expressed in various cell types including endothelial cells, stromal cells, immune cells, and cancer cells. A receptor subtype-selective drug targeting the receptor that is expressed on both cancer cells and stromal cells surrounding the tumor has a possibility causing different or opposite pharmacological effects. Thus, characterization and comprehensive understanding about each receptor subtype, receptor-associated proteins, and expression profiles of those molecules in each cell type is needed for predicting undesired side effects and maximizing therapeutic effects.

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Abbreviations:

ATX	autotaxin
COX	cyclooxygenase
DHA	docosahexaenoic acid
HDL	high density lipoprotein
EPA	eicosapentaenoic acid
HGF	hepatocyte growth factor
HIF	hypoxia-inducible factor
IL-8	interleukin-8
LPA	lysophosphatidic acid
LPP	lipid phosphate phosphatase
LPS	lipopolysaccharide
MMP	matrix metalloproteinase
SPHK	sphingosine kinase
SPP	S1P phosphatase
S1P	sphingosine 1-phosphate

TNF	tumor necrosis factor
VE	vascular endothelial
VEGF	vascular endothelial growth factor
VPF	vascular permeability factor
VSMC	vascular smooth muscle cell

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