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Autotaxin and LPA receptor signaling in cancer

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Abstract Lysophosphatidic acid (LPA; monoacyl-glycerol-3-phosphate) is a lipid mediator that functions as a mitogen and motility factor for many cell types. LPA signals through six specific G protein-coupled receptors, named $LPA_{1–6}$, which trigger both overlapping and distinct signaling pathways. LPA is produced from extracellular lysophosphatidylcholine by a secreted lysophospholipase D, named autotaxin (ATX), originally identified as an "autocrine motility factor" for tumor cells. ATX–LPA signaling is vital for embryonic development and promotes tumor formation, angiogenesis, and experimental metastasis in mice. Elevated expression of ATX and/or aberrant expression of LPA receptors are found in several human malignancies, while loss of LPA_6 function has been implicated in bladder cancer. In this review, we summarize our present understanding of ATX and LPA receptor signaling in cancer.

Keywords Autotaxin · Cancer · Lysophosphatidic acid · G protein-coupled receptor

1 Introduction

The impact of the tumor microenvironment on tumor progression is mediated, in large part, by growth factors, motility factors, and proangiogenic factors that are produced by the tumor cells themselves as well as the surrounding stroma. One such factor is lysophosphatidic acid (LPA; monoacyl-glycerol-3-phosphate), a multifunctional lipid mediator best known for its ability to stimulate proliferation, migration, and survival of many cell types, both normal and malignant. However, the list of biological responses to LPA is quite diverse, as it ranges from growth factor-like activities to neurite remodeling and modulation of ion channel activity [1, 2]. Bioactive LPA is produced extracellularly from lysophosphatidylcholine (an abundant plasma lipid) by a secreted lysophopholipase D (lysoPLD) [3, 4], known as autotaxin (ATX), named after its first discovered activity as an "autocrine motility factor" for melanoma cells [5]. LPA acts through six known G protein-coupled receptors (GPCRs), termed $LPA_{1–6}$, which are differentially expressed and show both overlapping and distinct signaling properties [1, 6]. A schematic representation of the ATX–LPA receptor signaling axis is shown in Fig. 1.

Increasing evidence points to an important role for ATX and LPA receptor signaling in cancer [7], as will be discussed below. In brief, (1) elevated or aberrant expression of ATX and LPA receptors is found in several human malignancies; (2) overexpression of ATX or individual LPA receptors promotes tumor formation and metastasis in mouse models, whereas knockdown has the opposite effect; and (3) LPA_2 knockout mice show reduced colon carcinogenesis. Moreover, loss of function of LPA_6 has been implicated in bladder cancer development, suggesting that LPA_6 is a candidate tumor suppressor. In this review, we summarize the evidence for a role of ATX–LPA signaling in cancer and also discuss recent developments in targeting ATX by pharmacological inhibitors.

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2 LPA receptor signaling

LPA receptors can be divided in two subfamilies. The classical $LPA_{1–3}$ receptors belong to the so-called endothe-

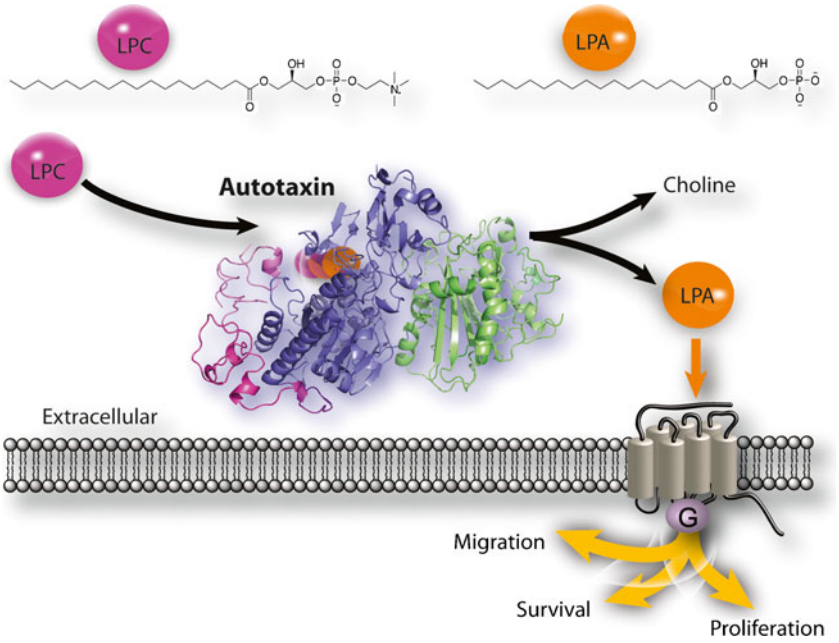

Fig. 1 Autotaxin–LPA receptor signaling. Autotaxin is a secreted lysophospholipase D that hydrolyzes extracellular lysophosphatidylcholine (an abundant plasma phospholipid) into bioactive LPA. LPA acts through specific G protein-coupled receptors and stimulates cell proliferation, migration, and survival. ATX is a multidomain enzyme; the colors refer to the specific domains (for structural details, see references [24, 25])

lial differentiation gene (Edg) family, whereas three additional LPA receptors ($LPA_{4–6}$) are more closely related to the purinergic receptor family [1, 6]. Depending on receptor subtype, LPA stimulation results in (1) activation of the mitogenic $G\alpha_i$-linked Ras-Raf-MEK-ERK pathway [8, 9]; (2) $G\alpha_i$-mediated activation of phosphoinositide 3-kinase-beta [10], which promotes cell survival and many other cellular functions; (3) cytoskeletal remodeling, cell migration and invasion via the $G\alpha_{12/13}$-linked RhoA pathway acting in concert with the $G\alpha_i$-mediated Rac activation pathway [11–13]; and (4) $G\alpha_q$-linked activation of phospholipase C with consequent production of second messengers [14, 15]. In addition, LPA stimulation often leads to changes in cAMP levels via either $G\alpha_i$ or $G(\beta\gamma)$ subunits (for review, see [1, 2]). LPA stimulation also promotes the production of growth factors and cytokines via multiple pathways [16]. For a given LPA receptor, the net outcome of these synergizing signaling pathways strongly depends on cellular context. For example, depending on the cell system used, LPA_4 receptor signaling may either enhance [17] or inhibit [18] tumor cell migration and invasiveness.

3 LPA production by autotaxin, a secreted lysoPLD

LPA is produced by autotaxin (ATX or ENPP2), a member of the ectonucleotide pyrophosphatase/phosphodiesterase (ENPP) family. The ENPP family consists of seven structurally related ectoenzymes that hydrolyze pyrophosphate and phosphodiester bonds in nucleotides and their derivatives [19]. ATX hydrolyzes LPC into LPA (plus free choline) and is the only lysoPLD in the ENPP family. ATX is synthesized as a preproenzyme, processed by a furin-type protease and secreted along the classical secretory route as a glycosylated protein into the extracellular milieu (reviewed in [20]). ATX is widely expressed and present in plasma. The origin of plasma ATX remains to be determined, but likely sources are the lymphatic high endothelial venules [21] and adipose tissue, which express and secrete ATX at high levels. Indeed, adipose-specific deletion of *Enpp2* leads to reduced plasma LPA levels [22].

ATX is a multidomain protein consisting of two N-terminal somatomedin B (SMB)-like domains, a central catalytic phosphodiesterase domain, and an N-terminal nuclease-like domain [19, 20]. Although ATX is capable of hydrolyzing nucleotides *in vitro*, the apparent affinity of ATX for LPC is some 10-fold higher than for nucleotides [23] and, furthermore, extracellular nucleotide levels are normally very low. Therefore, all biological effects of ATX are thought to be attributable to LPA production and subsequent receptor stimulation [20]. Formally, however, additional noncatalytic functions of ATX cannot be excluded at present. Recent structural studies [24, 25] have revealed how the different domains of ATX are organized and interact (Fig. 1) and shed light on what makes ATX a unique lysoPLD, namely a deep hydrophobic lipid-binding pocket in the catalytic domain. The ATX structure further suggests that the SMB domains could be involved in regulating catalytic activity [25].

3.1 ATX interaction with the cell surface

To ensure efficient delivery of LPA to its receptors, ATX must communicate with target cells in a locally restricted

manner. One mechanism by which ATX interacts with target cells is via integrins. ATX binds to activated lymphocytes via $\alpha_4\beta_1$ integrins [21] and to activated platelets via integrin β3 [26]. The SMB domains of ATX appear to be the primary mediators of integrin β3 binding [25]. Injection of enzymatically inactive ("dominant negative") ATX in mice attenuates the homing of T cells to secondary lymphoid organs, presumably by competing with endogenous ATX for binding to integrins [21]. Since ATX is abundantly expressed in lymphatic high endothelial venules (HEVs), this suggests a model in which secretion of ATX by HEVs promotes the entry of lymphocytes into lymphoid organs. In this model, ATX is secreted into the lumen of HEVs and binds to adherent lymphocytes through activated integrins. Subsequently, the lymphocyte-bound ATX may produce a high local concentration of LPA to activate LPA receptors on the lymphocytes and promote their transendothelial migration [21]. In support of this scenario, LPA induces invasion of T lymphoma cells across a monolayer of normal fibroblasts [12]. Thus, ATX/LPA could use a similar strategy to stimulate the extravasation of circulating tumor cells, a hallmark of the metastatic cascade.

Since ATX is a heparin-binding protein (as it can be purified using heparin affinity chromatography), binding to heparan sulfate proteoglycans (HSPs) on the cell surface could be an alternative or additional way by which ATX ensures local delivery of LPA to its cognate receptors. Thus, diverse scenarios for localized LPA production and signaling can be envisioned in which ATX is recruited to target cells via specific cell surface molecules such as integrins and HSPs.

4 ATX and LPA receptors in embryonic development

Gene targeting studies in mice have revealed a vital role for ATX during embryogenesis, as *Enpp2* knockout causes embryonic lethality at midgestation (around E9.5) due to severe vascular defects in both yolk sac and the embryo proper [27, 28]. The vascular network normally present in the yolk sac is completely absent and replaced by blood patches, while blood vessels in the embryo are enlarged; furthermore, the neural tube is malformed [27, 29]. Heterozygous *Enpp2*(+/−) mice show half-normal plasma LPA levels, consistent with ATX being the major LPA-producing enzyme in the circulation. The phenotype of *Enpp2*-knockout mice is strongly reminiscent of that of the $G\alpha_{13}$ knockout, suggesting that the observed defects in ATX-null embryos can be explained by loss of migratory G_{13}-RhoA signaling through multiple LPA receptors [27, 30].

The phenotype of individual LPA receptor knockouts is much less severe than that of the *Enpp2* knockout. Thus far, LPA receptor-knockout studies in mice have uncovered normal physiological roles for LPA signaling in such diverse processes as neurogenesis [31] and bone formation [32] (LPA_1), embryo implantation (LPA_3) [33], and formation of blood and lymphatic vessels (LPA_4) [34]. *Lpa*$_2$-knockout mice show no abnormalities [35], while the LPA_5- and LPA_6-deficient phenotypes remain to be described.

5 ATX–LPA receptor signaling in cancer

Since the discovery of ATX as an autocrine motility factor for melanoma cells, many subsequent studies have implicated a role for ATX–LPA signaling in tumor formation and metastasis.

5.1 Studies *in vitro*

High expression of ATX is found in a number of tumor cell types, including neuroblastoma [36], hepatocellular carcinoma [37], breast cancer [38], renal cell carcinoma [39], glioblastoma [40], non-small cell lung cancer (NSCLC) [41], B cell lymphomas [42, 43], and thyroid carcinoma [44]. Expression of ATX is found both in the tumor core as well as in the invasive cells of glioblastomas [40], and in NSCLC, the highest expression is detected in poorly differentiated tumors [41]. This argues that ATX is able to augment cellular characteristics necessary for tumor aggressiveness.

ATX expression is regulated by various growth factors, cytokines, and (proto-)oncogenes, which will differ per cell type and thus cause diverse outcomes. For example, EGF, bFGF, TGFβ, and other factors induce up- or down-regulation of ATX mRNA depending on cell type [44, 45]. v-Jun-transformed fibroblasts show strongly upregulated ATX expression [46], while ATX is upregulated in Wilms' tumors harboring oncogenic β-catenin mutations [47] and in mammary epithelial cells stimulated by Wnt-1 [48]. Downregulation of ATX is observed following retinoic acid treatment of Wilms' tumor cells and N-Myc-overexpressing neuroblastoma cells [49, 50].

In Hodgkin lymphoma cells, Epstein–Barr virus infection leads to strong induction of ATX expression, with subsequent generation of LPA and enhanced cell growth and survival [42]. Specific downregulation of ATX decreased LPA levels and reduced cell growth and viability in these cells. Furthermore, ATX expression is strongly induced upon forced expression of integrin α6β4 in MDA-MB-435 tumor cells, an effect mediated by the transcription factor NFAT1 [51]. This provides a possible explanation for the stimulatory effect of integrin α6β4 on tumor cell migration and invasion.

5.2 Insights from mouse studies

5.2.1 Xenograft models

The first evidence for a tumorigenic role of ATX *in vivo* came from studies using ATX-overexpressing, Ras-transformed NIH3T3 cells. ATX overexpression resulted in increased tumor growth, aggressiveness, and angiogenesis, whereas the inactive mutant ATX(T210A) did not [45, 52].

Subsequent studies have shown a role for both ATX and LPA receptor signaling in tumor progression and metastasis. LPA_1 overexpression in MDA-MB-231 breast cancer cells promotes increased skeletal tumor growth and tumor-induced bone destruction in xenografted mice. The tumor cells do not express ATX, but they stimulate the production of LPA by activated platelets, thereby promoting tumor cell proliferation and cytokine-mediated bone destruction [53]. Silencing or pharmacological inhibition of LPA_1 reduced both tumor growth and bone metastasis progression [54]. Furthermore, ATX overexpression in mammary carcinoma cells promotes metastasis to bone, while silencing of endogenous ATX expression inhibited metastasis, with little effect on primary tumor growth [55].

Forced overexpression of LPA_1, LPA_2, or LPA_3 in ovarian cancer cells enhances tumor growth in nude mice, showing increased growth factor production, ascites formation, and organ invasion [56]. In another study, overexpressed LPA_1, LPA_2, and LPA_4 were found to collaborate with c-Myc and Tbx2 (a transcriptional repressor of p19Arf) to transform mouse embryo fibroblasts (MEFs) both *in vitro* and in xenografts [57]. In this case, LPA-mediated cell transformation is mediated by the G_i-linked MAPK and PI3K pathways. Overexpression of individual LPA receptors in naïve MEFs had no transforming effect, indicating that LPA signaling needs to collaborate with other pro-oncogenic events to induce cell transformation [57].

5.2.2 Genetic models

Unfortunately, the embryonic lethality of ATX-deficient mice has hampered studies on the importance of ATX in cancer progression. However, important insights have been gained form studies in transgenic and LPA receptor-knockout mice. MMTV-driven overexpression of ATX or individual LPA receptors ($LPA_{1–3}$) in mouse mammary gland leads to late-onset invasive and metastatic mammary carcinomas and cancer-associated inflammation [58]. The transgene expression influenced several signaling pathways, including PI3K-Akt and MAPK pathways, as well as Wnt pathway components and E-cadherin. The ATX and LPA receptor-driven tumors do not form a distinct cluster, as would be expected due to the fact that each of the receptors links to particular pathways and functional outcomes [58]. This reinforces the notion that transgenic overexpression of ATX and LPA receptors allows accumulation of secondary mutations leading to mammary cancers, possibly by increasing cell viability upon LPA signaling and thus increasing the likelihood of acquiring (pro-) oncogenic mutations.

Of the known LPA receptors, LPA_2 has been implicated in intestinal cancer [59]. In a model of chemically induced colon carcinogenesis, LPA_2-knockout mice (which show a wild-type phenotype) display a remarkably reduced tumor incidence and progression. This is accompanied by a decrease in both cell proliferation and chemokine expression, in particular the proinflammatory factors MCP-1 and MIF which are associated with colorectal cancer. Reduced colon tumorigenesis in the LPA_2-null animals correlated with reduced infiltration by macrophages [59], a predominant stromal cell type known to contribute to tumor progression. Furthermore, LPA treatment increased tumor incidence in $APC^{min/+}$ mice, a model for spontaneous intestinal cancer [59]. Conversely, loss of LPA_2 dramatically reduced tumor incidence in $APC^{min/+}$ mice, accompanied by reduced expression levels of cell cycle regulators such as KLF5, c-Myc, and cyclin D1 [60]. These studies show that LPA_2, in combination with loss of the tumor suppressor APC, is capable of promoting tumorigenesis in the colon. It thus appears that, again, LPA signaling increases the susceptibility to accelerate cancer progression when other genetic factors are present. The results from the various *in vivo* studies are summarized in Table 1.

6 Clinical implications

To what extent do the findings obtained in mouse models bear relevance to the human disease? Cancer-specific gain-of-function mutations in ATX or LPA receptors have not been reported to date; in contrast, loss of function mutations have been reported for LPA_6 in bladder cancer (see below). Analysis of multiple microarray datasets (www.oncomine.org) reveals strongly elevated ATX expression in certain human cancers, especially B cell lymphomas, renal carcinoma, liver cancer, and pancreatic cancer. Also, individual LPA receptors are found overexpressed in several cancers when compared to the corresponding normal tissues (www.oncomine.org, see also [7]).

In follicular lymphoma, serum ATX levels correlate with tumor burden and clinical course, suggesting that ATX may serve as a biomarker in follicular lymphoma [43]. Furthermore, an increase in serum ATX activity has been reported in pancreatic cancer patients [61] and *ENPP2* is one of the genes in a 64-gene signature that predicts poor survival of patients with stage I NSCLC [62]. As a word of caution, it

Table 1 *In vivo* ATX and LPA receptor cancer models

		Model	System	Remarks	Phenotype	References
ATX overexpression		Xenograft	NIH3T3 cells (Ras transformed)	v-Ras dependent	Increased tumorigenesis, metastasis and angiogenesis	[45, 52]
		Transgene	Mammary gland	MMTV driven	Induction of invasive and metastatic mammary cancer	[58]
		Xenograft	Human breast cancer (MDA-MB231 metastatic subclone)		Enhanced tumor growth and metastasis to bone	[55]
ATX knockdown		Xenograft	Mouse mammary tumor cells (4T1)		Reduced bone metastasis (unaffected primary tumor growth)	[55]
LPA receptor overexpression	LPA_{1-3}	Xenograft	Ovarian cancer cells		Increased tumor growth, invasion, cytokine production and ascites formation	[56]
	$LPA_{1,2,4}$	Xenograft	Mouse embryonic fibroblasts	Myc dependent	Induction of tumor formation	[57]
	LPA_1	Xenograft	Human breast cancer cells (MDA-MB231 metastatic subclone)	Involvement of platelets	Enhanced tumor formation and metastasis to bone	[53, 54]
LPA receptor knockdown	LPA_1	Xenograft	Human breast cancer cells (MDA-MB231 metastatic subclone)	Reproduced by LPA1 antagonist Ki16425	Reduced tumor growth and metastasis to bone	[54]
	LPA_{1-3}	Transgene	Mammary gland	MMTV driven	Induction of invasive and metastatic mammary cancer	[58]
LPA receptor knockout	LPA_2	Knockout	Chemically induced colon cancer model		Reduced tumor incidence; less macrophage infiltration	[59]
	LPA_2	Knockout	APC(min/+) intestinal cancer model		Reduced tumor incidence	[60]

should be realized that high ATX expression by itself does not necessarily imply elevated LPA levels and enhanced receptor signaling, since substrate (LPC) availability and LPA degradation by cell-associated lipid phosphate phosphatases are additional determinants of bioactive LPA levels in the cellular microenvironment [20]. Ultimately, it is the LPA receptor expression profile on both the tumor and surrounding stromal cells that will determine the outcome of enhanced ATX expression. One area of future research is to establish to what extent aberrant ATX and/or LPA receptor expression patterns are associated with clinical outcome.

6.1 LPA_6: a candidate tumor suppressor in bladder cancer

The LPA_6 receptor, previously known as orphan receptor P2Y5 (or 6H1), deserves special mention because it has been associated with familial bladder cancer [63] as well as genetic hair growth abnormalities [64]. LPA_6/P2Y5 is known to couple to the $G\alpha_{13}$-RhoA signaling pathway, which regulates the actin cytoskeleton, but it does not mediate changes in cytosolic calcium or cAMP [65]. *P2RY5* is an inducible gene: its expression is rapidly induced upon T cell activation [66] and in LPA-stimulated fibroblasts [16].

The LPA_6-encoding gene, *P2RY5*, is located inside the retinoblastoma tumor suppressor gene *RB1* (intron 17) in the reverse orientation. In bladder cancer, a segment around *RB1* is characterized by a loss of polymorphism associated with the initial expansion of neoplasia [63, 67]. This segment contains several so-called forerunner genes that may contribute to such expansion, and *P2RY5* is one of these genes. Homozygous mutational inactivation of *P2RY5* precedes the loss of *RB* during tumor development, while nucleotide substitutions in *P2RY5* represent a cancer-predisposing factor, particularly in combination with tobacco smoking [63, 67]. Reintroduction of *P2RY5* into bladder cancer cells that lacked it resulted in cell cycle arrest and apoptosis, consistent with *P2RY5* being a candidate tumor suppressor. One family with an inherited risk of cancer, including breast, colon, lung, prostate, and uterus, carried a germline mutation in *P2RY5*. The most frequent polymorphism results in a W307C mutation in the LPA_6 cytoplasmic tail. This could affect LPA_6 interaction with G proteins

[63, 67] and hence compromise LPA signaling, but this needs to be tested. Interestingly, a single nucleotide polymorphism within the same genomic locus that is predicted to downregulate *P2RY5* expression is a potential risk factor for developing invasive ovarian cancer [68].

Loss of *P2RY5* function has also been implicated in genetic hair growth disorders [64]. LPA_6/P2Y5 is detected in the inner root sheath of hair follicles. However, human hair follicles do not express ATX but, instead, an LPA-producing phospholipase A1 encoded by *LIPH* [69]; mutations in *LIPH* induce the same abnormal hair growth phenotype as mutations in LPA_6. This raises the question of whether LPA_6 in other tissues, such as bladder epithelium, is normally stimulated via ATX- or LIPH-mediated LPA production. Given the very restricted tissue distribution of LIPH, however, ATX is the more attractive candidate.

In conclusion, *LPA_6/P2RY5* provides a new paradigm for cancer development and may represent an early detection and risk marker in bladder cancer [70]. It is now important that the biological function and signaling properties of LPA_6 and its mutant versions be elucidated in further detail.

7 ATX as a drug target

As a secreted phosphodiesterase, ATX is an attractive and easily "druggable" therapeutic target. Several ATX inhibitors have been based on the seminal finding that LPA and sphingosine 1-phosphate (S1P) inhibits ATX activity against nucleotides and artificial substrates (K_i about 100 nM) [23]. Several LPA analogs have been described as ATX inhibitors, some with an effect on melanoma cell metastasis [71, 72] and breast tumor growth in mice [73]. Yet, the potency of LPA analogs is rather low (and even very poor when tested in ATX-mediated LPC hydrolysis assays), and it is not clear whether the reported *in vivo* effects are attributable to ATX inhibition. Most LPA-based ATX inhibitors lack an *in vivo* pharmacodynamic proof of principle in that they have not been shown to lower circulating LPA levels. Furthermore, there are concerns about their potential agonistic effect on LPA receptors. FTY720, a structural analog of sphingosine, is an immunomodulator for patients with relapsing multiple sclerosis. The active form, FTY720-phosphate (FTY-P) is an S1P mimetic and acts on S1P receptors with high potency. At higher concentrations, FTY-P (like S1P) is a competitive inhibitor of ATX and reduces plasma LPA levels when injected into mice [74]. It remains to be seen, however, whether ATX inhibition underlies the reported anticancer effects of high doses FTY720 [74]. Lipid phosphonate analogs that inhibit ATX activity against artificial substrates show a reducing effect on plasma LPA levels and B16 melanoma metastasis; however, their potency is relatively low [75].

Nonlipid, small-molecule inhibitors clearly hold more promise. High-throughput screening identified thiazolidinedione-based compounds as a new class of ATX inhibitors [76]. Their potency is increased dramatically by introduction of a boronic acid moiety, designed to target the catalytic Thr residue in ATX. The most potent analogs show IC_{50} values <10 nM in LPC hydrolysis assays [76, 77]. Injection of these compounds into mice results in a rapid fall in circulating LPA levels, consistent with LPA being rapidly produced and degraded *in vivo*. The crystal structure of the ATX in complex with a boronic acid inhibitor reveals that it forms a reversible covalent bond with the Thr210 nucleophile in the hydrophobic lipid-binding pocket of ATX [25]. Another small-molecule inhibitor of ATX, PF-8380, shows adequate oral bioavailability and *in vivo* potency in reducing LPA levels in plasma and at sites of inflammation [78], indicating that ATX is a major source of LPA during inflammation. Furthermore, a close pharmacokinetic/pharmacodynamic relationship was observed. Compounds like PF-8380 can serve as useful tools for elucidating the role of ATX in tumor progression in mice.

8 Concluding remarks

Given its mitogenic and chemotactic properties, together with the wide distribution of LPA receptors, it is not surprising that LPA, when produced in the tumor–stroma microenvironment, can enhance cancer progression. Although the clinical consequences of enhanced or aberrant LPA production and signaling remain to be determined, studies in mice have provided strong evidence that the ATX–LPA receptor signaling axis contributes to tumor formation, angiogenesis, and metastasis. The *in vivo* studies also indicate that distinct oncogenic events, such as H-Ras or c-Myc activation, must collaborate with LPA signaling to promote tumor progression. The LPA_2 receptor provides perhaps the strongest case for a link between LPA signaling and cancer, since *Lpa_2*-knockout mice show a marked decrease in colon tumor incidence. Additional evidence is provided by the study on transgenic overexpression of ATX and LPA receptors in mouse mammary gland. To more broadly assess the importance of LPA signaling in tumor maintenance and progression, a logical approach would be to crossbreed LPA receptor-null mice with genetically engineered mouse tumor models, in which cancer is initiated by *Cre*-recombinase-mediated activation of oncogenic mutations in specific tissues.

The LPA_6 receptor represents an interesting case, since it may function as a tumor suppressor in familial bladder cancer and loss of function mutations have been detected in

patients; nucleotide substitutions in the LPA_6-encoding gene (*P2RY5*) are considered a cancer-predisposing factor. Obviously, these intriguing findings require further validation and investigation. *Lpa_6*-knockout mice will provide a powerful tool to examine the suspected tumor-suppressing function of LPA_6.

Hopefully, the knowledge on ATX–LPA signaling gleaned in academic labs can now be applied toward the development of new drugs for cancer treatment in the foreseeable future. That ATX is an extracellular enzyme and GPCRs, such as those for LPA, are highly druggable will add to their attractiveness as targets. Potent small-molecule inhibitors that target ATX *in vivo* have already been described. Now that the crystal structure of ATX has been determined, drug development efforts will undoubtedly get a further boost.

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