Review Article

Autotaxin and Lysophosphatidic Acid Signalling: the Pleiotropic Regulatory Network in Cancer

(autotaxin / ENPP2 / lysophosphatidic acid / LPA / signal transduction / cancer)

ONDŘEJ VÍT, JIŘÍ PETRÁK

BIOCEV, First Faculty of Medicine, Charles University, Vestec, Czech Republic

Abstract. Autotaxin, also known as ecto-nucleotide pyrophosphatase/phosphodiesterase family member 2, is a secreted glycoprotein that plays multiple roles in human physiology and cancer pathology. This protein, by converting lysophosphatidylcholine into lysophosphatidic acid, initiates a complex signalling cascade with significant biological implications. The article outlines the autotaxin gene and protein structure, expression regulation and physiological functions, but focuses mainly on the role of autotaxin in cancer development and progression. Autotaxin and lysophosphatidic acid signalling influence several aspects of cancer, including cell proliferation, migration, metastasis, therapy resistance, and interactions with the immune system. The potential of autotaxin as a diagnostic biomarker and promising drug target is also examined.

Introduction

Autotaxin (ATX) is a secreted glycoprotein that hydrolyses lysophosphatidylcholine (LPC) and other glycerophospholipids into lysophosphatidic acid (LPA) (Fig. 1) (Aoki et al., 2002; Tokumura et al., 2002; Umezu-Goto et al., 2002). LPA is a signal transduction ligand recognized by specific G protein-coupled receptors on the cell membrane (Goetzl and An, 1999; Tigyi, 2010). The lysophospholipase D (lysoPLD) activity of the protein is responsible for most of the extracellular LPA, and ATX is therefore recognized as a "gatekeeper" of LPA signalling control (Brindley et al., 2013). Binding of LPA to its receptors activates numerous signal transduction pathways, including pro-survival phosphoinositide 3-kinase (PI3K) pathways, mitogen-activated protein kinase (MAPK), Rho A-dependent cytoskeletal remodelling, or production of second messengers through phospholipase C (PLC) (summarized in Anliker and Chun, 2004; Lin et al., 2010; Yung et al., 2014).

ATX is a member of the ecto-nucleotide pyrophosphatase/phosphodiesterase (ENPP) protein family and its recommended name according to the Uniprot database is "ectonucleotide pyrophosphatase/phosphodiesterase family member 2" (hence the gene name *ENPP2*). ATX is, however, the only member of the family with lysoPLD activity. The remaining members mainly metabolize extracellular nucleotides or, in the case of ENPP1, regulate bone calcification through the release of pyrophosphate ions (Goding et al., 2003).

ATX gene, splice variants and protein structure

ATX is encoded by the *ENPP2* gene located on human chromosome 8 at position 8q24.1. The gene contains 27 exons, and at least five splice variants designated ATXα through ATXε are generated by alternative splicing. The ATXβ splice variant, or "teratoma ATX", was found in a teratocarcinoma cell line (Lee et al., 1996), codes for an 863 amino acid-long polypeptide, and is considered the canonical sequence in genomic and protein databases. The first described splice variant was ATXα, encoding a 915 amino acid-long polypeptide also known as "melanoma ATX" (Stracke et al., 1992). Compared with ATXβ, it contains a polypeptide sequence encoded by exon 12. The third variant, representing 888 amino acid-long ATXγ, contains an additional sequence of exon 21 (Giganti et al., 2008), which is missing in all other splice variants (Fig. 2).

Human ATXα has relatively low expression and is present in both central nervous system and non-neural

Received December 19, 2023. Accepted December 22, 2023.

Corresponding author: Ondřej Vít, BIOCEV, First Faculty of Medicine, Charles University, Průmyslová 595, 252 50 Vestec, Czech Republic. Phone: +420 325 873 010; e-mail: ondrej.vit@lf1.cuni.cz

This study was supported by the Czech Agency for Healthcare Research (NU23-01-00323), by the Ministry of Education, Youth, and Sports of the Czech Republic via Charles University (UNCE/MED/016 and the Cooperatio programme, research area BIOLOGY), and by the National Institute for Cancer Research (Reg. No. LX22NPO5102) funded by the European Union – Next Generation EU, Programme EXCELES.

Abbreviations: ATX – autotaxin, EMT – epithelial-mesenchymal transition, HCC – hepatocellular carcinoma, LPA– lysophosphatidic acid, LPC – lysophosphatidylcholine, LPP – lipid phosphate phosphatases, lysoPLD – lysophospholipase D, MAG – monoacylglycerol, NLD – nuclease-like domain, PDE – phosphodiesterase domain, SMB1, SMB2 – somatomedin B-like domains.

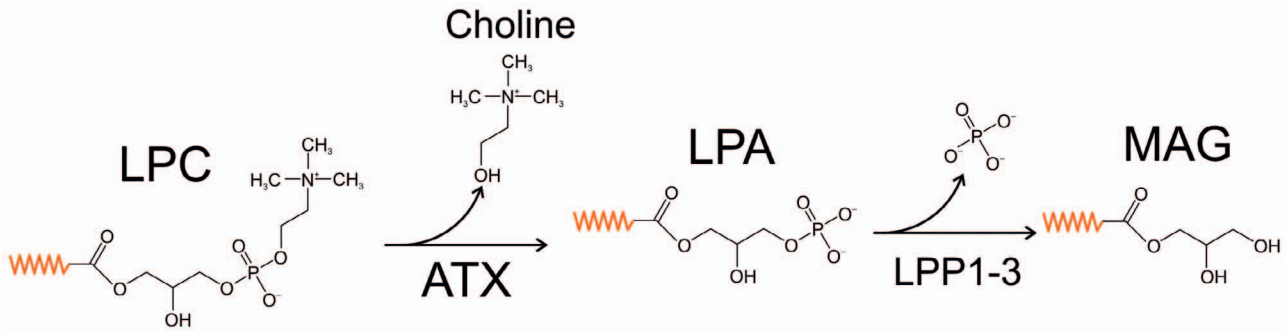

Fig. 1. The enzymatic activity of ATX. Lysophosphatidylcholine (LPC) is cleaved into lysophosphatidic acid (LPA), which can act as a signal molecule, and choline. LPA is degraded by lipid phosphate phosphatases 1–3 (LPP1-3), which dephosphorylate LPA and generate monoacylglycerol (MAG) to be utilized elsewhere.

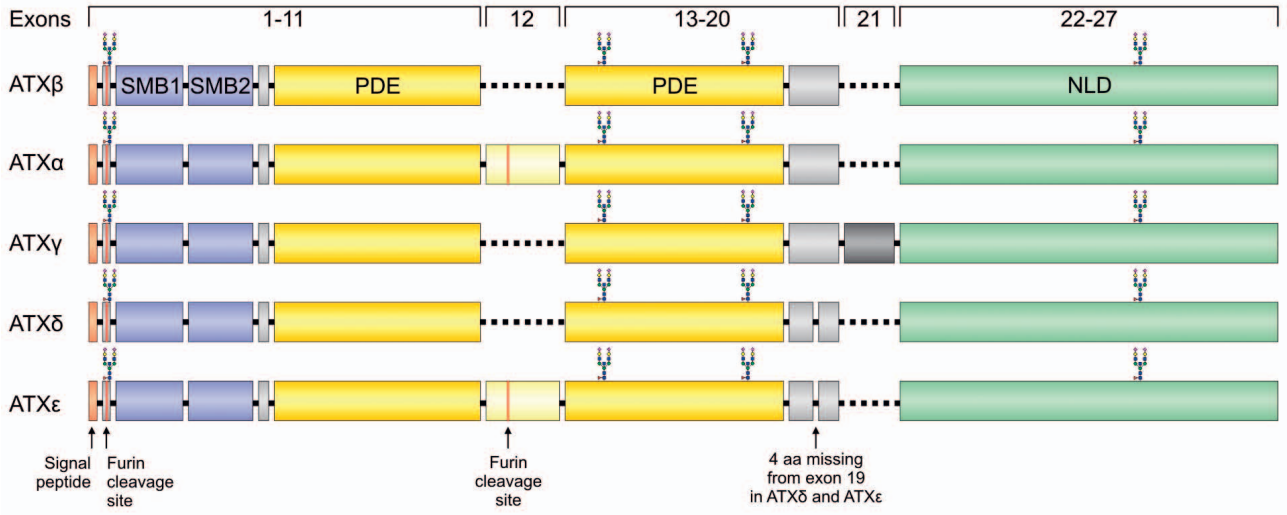

Fig. 2. Overview of the five protein isoforms of ATX generated by alternative splicing. The exons that encode the respective segment of the protein are indicated above. SMB1, SMB2: somatomedin B-like domains. PDE: phosphodiesterase domain. NLD: nuclease-like domain. N-glycosylated sites are marked by symbols of a branched oligosaccharide. The light yellow section of the PDE domain indicates the polybasic insert in ATXα and ATXε encoded by exon 12. The dark grey section in ATXγ symbolizes the sequence encoded by exon 21. Dashed lines represent the sequence encoded by the omitted exons.

tissues (adipose tissue, heart, kidney, liver, pancreas), while the expression of ATXβ is found mainly in non-neural tissues and is the predominant isoform detected in the plasma (Tokumura et al., 2002). ATXγ is expressed mainly in the central nervous system and comprises the vast majority of ATX in the brain (Giganti et al., 2008). The most recently described splice variants ATXδ and ATXε are identical to ATXβ and ATXα, respectively, but both miss the same four amino acids in the sequence corresponding to exon 19 (Hashimoto et al., 2012; Barbayianni et al., 2015).

The domain structure of the ATX protein is common among the closest relatives of ATX, i.e., ENPP1 and ENPP3 (Goding et al., 2003; Stefan et al., 2005). From the N-terminus, it contains two somatomedin B-like domains (SMB1, SMB2), the central catalytic phosphodiester (PDE) domain, and the nuclease-like domain (NLD) at the C-terminus. Unlike ENPP1 and ENPP3, ATX lacks an N-terminal transmembrane domain. Instead, it has a signal peptide that is cleaved post-translationally and an additional furin cleavage site (following a propeptide sequence) in the N-terminal region (Jansen et al., 2005). Similarly to most extracellular proteins, ATX is N-glycosylated on multiple asparagines (N54, N411, N525, and N807 according to Uniprot). The N-glycosylation at N525 at the C-terminal part of the catalytic domain is crucial for the enzymatic activity of ATX and is present inside the folded protein (Jansen et al., 2007). N54 and N411 are indispensable for ATX secretion (Pradère et al., 2007).

The SMB1 and SMB2 domains are rich in cysteines and are critical for interaction of ATX with integrins

(Hausmann et al., 2011). Through these domains alone (even after inhibition of the lysoPLD activity of the enzyme), ATX promotes persistent directional migration of cells (Wu et al., 2014). Even a single SMB domain is sufficient for this ATX activity.

The catalytic PDE domain is sequentially and structurally related to alkaline phosphatases, harbouring two zinc atoms (Hausmann et al., 2011; Nishimasu et al., 2011). The catalytic mechanism is also similar (Stefan et al., 2005): the metal-activated OH group of threonine 210 attacks the phosphate group of substrate LPC and forms a phosphate ester; then, LPA is released through a second attack by a second metal-activated water molecule (Stefan et al., 2005).

In the central part of the PDE domain of ATXα and ATXε variants, corresponding to the sequence of exon 12, there is a polybasic insert that contains a cleavage site for endogenous extracellular furin-like endoproteases. This cleavage causes instability of the protein *in vitro* (Giganti et al., 2008; Hashimoto et al., 2012), but the presence of this sequence also promotes binding of ATXα to cell surface heparan sulphate proteoglycans. Binding to the proteoglycans is preserved even after the cleavage, as the protein remains intact due to disulphide bonds. This interaction not only targets LPA production to the cell surface but also stimulates the lysoPLD activity of ATX (Houben et al., 2013).

The nuclease-like domain at the C-terminus of ATX is structurally related to non-specific RNA and DNA endonucleases (Gijsbers et al., 2001). While it lacks any enzymatic activity in ATX, it is needed for proper folding of the protein. There is a disulphide bond between the catalytic and nuclease-like domain, which is essential for the enzyme function. Residues 829–850 are needed for secretion of ATX; without this sequence, ATX tends to accumulate in the Golgi apparatus (Jansen et al., 2009).

Regulation of ATX gene expression

The control of *ENPP2* gene expression relies on various transcription factors, namely HOXA13 (Williams et al., 2005), NFAT transcription factor family (Chen and O'Connor, 2005), STAT3 (Azare et al., 2011), JUN (Sioletic et al., 2014), HIF1-α (Farquhar et al., 2017), β-catenin (Sah et al., 2020; He et al., 2021), several FOX family transcription factors (Cao et al., 2020; Xie et al., 2020; He et al., 2021), and E2F7 (Lin et al., 2023) in various tissues, and depending on physiological constellations.

Histone deacetylases were shown to regulate *ENPP2* expression: HDAC3 and HDAC7 repress its expression in cancer cells (Li et al., 2011). In breast cancer, promoter methylation represses *ENPP2* expression (Panagopoulou et al., 2022). Under hypoxia, histone crotonylation of the *ENPP2* promoter region, dependent on HIF-2α, results in ATX up-regulation (Qu et al., 2023). Some histone demethylases promote transcription of *ENPP2*: through histone demethylation as with H3K27me3 demethylase UTX, or non-enzymatically as with H3K27me3 demethylase KDM6B with cooperation of DDX21 helicase (Argaud et al., 2019).

The expression of *ENPP2* is also regulated post-transcriptionally. Endogenous miRNAs participate in the process (Murph, 2019), including miR-101-3p that targets *ENPP2* mRNA for degradation (Wang et al., 2019). RNA-binding proteins also play a role, namely AUF1 and HuR, which both bind the 3'-untranslated region and either promote mRNA decay (AUF1) or stabilize it (HuR) (Sun et al., 2016) by methylation of the 3'-UTR of *ENPP2* mRNA (Xu et al., 2020).

Secretion of ATX

ATX is secreted after its processing in the Golgi apparatus. It is synthetized as a pre-pro-enzyme, and two cleavages (the signal peptide and an additional N-terminal furin cleavage site) occur prior to the ATX secretion (Jansen et al., 2005). N-glycosylation and cleavage of the signal sequence are both critical for secretion of ATX, while the furin cleavage does not seem to directly affect the secretion neither the biologic activity of ATX (Pradère et al., 2007).

Secreted ATX interacts with cell-surface integrins (Kanda et al., 2008; Hausmann et al., 2011; Wu et al., 2014), or heparan sulphate proteoglycans in the case of ATXα (Houben et al., 2013), and also with syndecan-4 in the case of ATXβ (Leblanc et al., 2018). These interactions seem to localize the ATX molecule and LPA production close to the plasma membrane, to the vicinity of the LPA receptors (Fulkerson et al., 2011; Moolenaar and Perrakis, 2011; Leblanc et al., 2018). The cell surface localization of ATX was demonstrated using immunofluorescence by Kanda et al. (2008) on lymphocytes. However, it remains to be determined what fraction of secreted ATX is cell surface bound, whether the binding is tissue specific and whether it is a regulated process dependent on physiological constellation.

Functions of ATX

As mentioned in the introduction, the first discovered enzymatic functions of ATX were nucleotide-related enzymatic activities, namely pyrophosphatase, phosphodiesterase, and ATPase activities. These were proposed based on its homology with mouse ectonucleotide pyrophosphatase/phosphodiesterase family member 1 (ENPP1) and verified *in vitro* (Murata et al., 1994). Nevertheless, the lysoPLD activity of ATX is the main physiological function of ATX in the mammalian body (Tokumura et al., 2002; Umezu-Goto et al., 2002).

The key threonine residue T210 in the catalytic domain, which provides transient covalent binding of reaction intermediates (Clair et al., 1997; Stefan et al., 2005), ensures both the nucleotide-related and lysoPLD enzymatic activities. Divalent cations including Ca^{2+}, Mg^{2+} (Lee et al., 2001), but *in vivo* usually Zn^{2+} (Hausmann et al., 2011; Nishimasu et al., 2011), are essential for all enzymatic activities of ATX (Lee et al., 2001; Giganti et al., 2008).

In addition to ATX, LPA can also be produced by secretory phospholipases A1 and A2. However, it was shown that mice heterozygous for ATX ($Enpp2^{+/-}$) produced approximately half of the LPA plasma levels compared to wild-type mice (Tanaka et al., 2006; van Meeteren et al., 2006). Similarly, treatment of mice with ATX inhibitors leads to severe reduction in LPA plasma levels (Albers et al., 2010a; Benesch et al., 2014). These observations clearly suggest that ATX is the main enzyme responsible for circulating LPA. The LPA produced by ATX is further hydrolysed to monoacylglycerol (Fig. 1) by three lipid phosphate phosphatases (LPP1-3), also located on the cell surface (Tang et al., 2015). The turnover of LPA in the blood can be strikingly rapid, as shown in experiments with the ATX inhibitor, indicating that both ATX and LPPs (Fig. 1) and the balance of their respective activities determine the actual level of LPA in the bloodstream (Albers et al., 2010a).

Upon the binding of LPC, ATX executes its lysoPLD activity, but the release of LPA is very slow, as it happens in the range of tens of seconds up to several minutes. This observation led Sauders et al. (2011) to hypothesize that in addition to its enzymatic activity, ATX may serve as a LPA chaperone or carrier, enabling its delivery to remote locations and preventing its degradation. However, whether ATX actually plays such a role remains to be determined.

The signalling network of LPA

ATX-generated LPA is an important signal molecule with a pleiotropic effect. LPA in the extracellular space or in circulation binds to and activates six different G protein-coupled receptors designated LPAR1–6 or $LPA_{1–6}$. These receptors trigger (via various G proteins) multiple signalling pathways, including those initiated by Rho small GTPases, adenylyl cyclase, phospholipase C, phosphoinositide 3-kinases/Akt, or MAP kinases (ERK) (Yung et al., 2014) (Fig. 3). The biological effects of LPA signalling is therefore highly diverse and depends on the cellular LPA receptor repertoire, G-protein type involved, tissue type, and biological context (Choi et al., 2010; Yung et al., 2014). While LPARs 1–3 typically act as pro-proliferation stimuli and enhance cell motility, LPARs 4–6 can be generally characterized as suppressive for migration and invasion; however, again depending on the actual biological context (Lee et al., 2008; Jongsma et al., 2011; Ishii et al., 2015; Takahashi et al., 2017).

The engagement in the multitude of signalling pathways makes the ATX-LPA axis an active regulatory element in numerous highly diverse physiological and pathological processes, including the immune response, inflammation, fibrosis, tissue remodelling, and many others. However, our understanding of the role LPA plays in these complex processes remains limited.

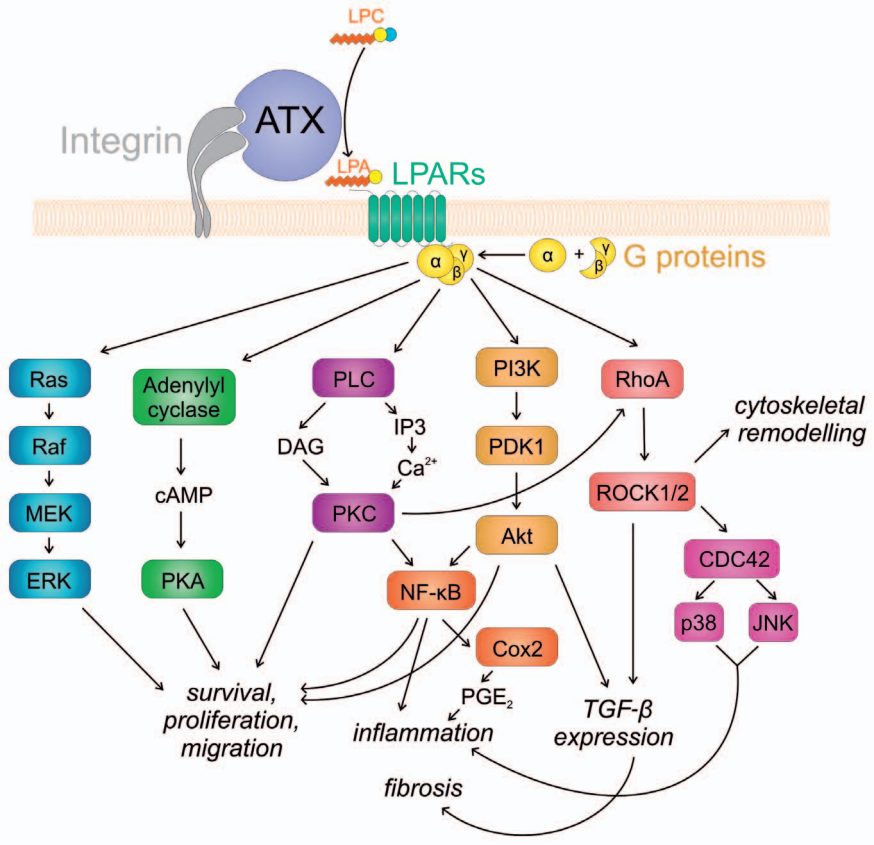

Fig. 3. Simplified summary of ATX and LPA signalling. LPA receptors (LPARs) initiate the signalling via various G proteins. For simplicity, only the well-documented signalling pathways discussed in the text are shown.

In addition to the complex network of LPA-based signal transduction, ATX seems to play an LPA-independent role in the regulation of cell processes, at least *in vitro*. It was demonstrated that ATX alone in the absence of LPA, or devoid of its enzymatic activity, could promote cell migration upon binding to cell membrane integrins *in vitro* (Wu et al., 2014). Whether this phenomenon plays some role *in vivo*, whether it is coupled to a distinct intracellular signalling pathway via the integrin molecules, or whether it represents another process remains to be determined.

Autotaxin in human physiology

The regulatory role of ATX starts at early embryonic development, namely, in orchestration of angiogenesis (Tanaka et al., 2006; van Meeteren et al., 2006), neural tube formation (van Meeteren et al., 2006; Fotopoulou et al., 2010), and haematopoiesis (Li et al., 2014). In mice, *Enpp2* knock-out or inactivation of its enzymatic activity are embryonically lethal due to the inability to form mature blood vessels (Tanaka et al., 2006; van Meeteren et al., 2006; Ferry et al., 2007). Surprisingly, in adult mice, ATX is dispensable, as shown using inducible genomic deletion (Katsifa et al., 2015).

The most important roles of the ATX-LPA axis in adult physiology are integrated in the complex process of wound healing. ATP and LPA participate in the process by modulating the inflammatory response and extracellular matrix remodelling, essential for tissue repair and regeneration. LPA activates platelets and has chemoattractant and growth factor properties (Balazs et al., 2000). It also acts as a mitogen in fibroblasts (van Corven et al., 1992) and participates in collagen deposition into the extracellular matrix (Chabaud et al., 2015). LPA stimulates inflammation though multiple pathways including PI3K, PKA, MAP, and Rho kinases, resulting in expression of cytokines (Liu et al., 2009a) and lymphocyte homing through a yet not well understood mechanism (Knowlden and Georas, 2014). Furthermore, LPA also facilitates angiogenesis through LPAR1- and LPAR3-initiated signalling (Rivera-Lopez et al., 2008).

The ATX-LPA axis plays a significant part in inflammation and immune system regulation in several ways (Sevastou et al., 2013). LPA regulates both innate and adaptive immune responses – for instance, it can directly activate CD4 T cells to proliferate. ATX also promotes T-lymphocyte migration through locally generated LPA (Georas, 2009), and ATX and LPA promote lymphocyte homing to secondary lymphoid organs (Kanda et al., 2008). Further effects of the ATX-LPA axis in the immune response include extravasation of lymphocytes through basal lamina of lymphatic vessels (Bai et al., 2013), trans-endothelial migration of T lymphocytes (Zhang et al., 2012), motility of T lymphocytes inside the lymph node (Takeda et al., 2016), and transformation of monocytes to macrophages initiated by activation of Akt/mTOR pathways (Ray and Rai, 2017).

In adults, ATX also plays a role in adipose tissue expansion and influences energy expenditure via glucose and lipid homeostasis (Jose and Kienesberger, 2021). ATX is highly expressed and secreted by adipocytes; in fact, adipose tissue is the main source of circulating ATX. Increased expression of ATX in obese patients and mouse models of obesity has been reported (Jose and Kienesberger, 2021). Adipocyte-specific *Enpp2* knock-out mice fed a high-fat diet showed smaller body weight gains and less insulin resistance than control mice fed the same diet (Nishimura et al., 2014). ATX seems to connect obesity and insulin resistance with inflammation, as it was shown that inflammatory mediators, namely IL-6, increase ATX expression in adipocytes, which in turn contributes to insulin resistance in a mouse model of obesity (Sun et al., 2017).

The regulation of such complex and diverse physiological processes by ATX and LPA is indeed mirrored in numerous human diseases. Cancer is the one in the spotlight of this review.

ATX, LPA and cancer

Because of frequent up-regulation of ATX in cancer cells or tumours and due to the multiple effects of the ATX-LPA axis, namely pro-proliferative, pro-migratory, and pro-inflammatory, the ATX-LPA tandem has attracted massive attention of researchers in the field.

Genomic data show that *ENPP2* gene amplification is frequent in many types of cancer including ovarian cancer, breast cancer, hepatocellular carcinoma, urothelial bladder cancer, head and neck squamous cell carcinoma, or lung adenocarcinoma (Gao et al., 2013; Federico et al., 2016).

Up-regulation of *ENPP2* mRNA expression has been observed in melanoma cells (Stracke et al., 1992), non-small-cell lung cancer (Yang et al., 1999), renal cancer (Stassar et al., 2001), thyroid carcinomas (Kehlen et al., 2004), hepatocellular carcinoma (Cooper et al., 2007), prostate cancer (mRNA) (Nouh et al., 2009), glioblastoma multiforme (Hoelzinger et al., 2005), and endometrial cancer (Mazzocca et al., 2018). Up-regulation of the ATX protein or its increased enzymatic activity has been reported in glioblastoma multiforme (Hoelzinger et al., 2005), ovarian cancer (Tokumura et al., 2007), follicular lymphoma (Masuda et al., 2008), prostate cancer (Nouh et al., 2009), pancreatic cancer (Nakai et al., 2011), renal carcinoma, bladder carcinoma (Xu et al., 2016), breast cancer (Shao et al., 2019), and recently also in pheochromocytoma and paraganglioma (Vít et al., 2023).

As a result of increased ATX activity, increased LPA was also reported in numerous cancer types (Masuda et al., 2008; Nakai et al., 2011; Patterson et al., 2011; Zeng et al., 2017).

Elevated expression of LPA receptors (either mRNA or protein) was observed in cancer patients. This is especially relevant with LPAR1, LPAR2 and LPAR3, which positively regulate cell proliferation and migration: LPAR1 expression was found to be increased in glioblastoma (Kishi et al., 2006) and hepatocellular carcinoma (Park et al., 2011), LPAR2 in colon cancer (Shida

et al., 2004), and LPA3 in hepatic cancer (Zuckerman et al., 2016), to mention just a few examples.

Although observed frequently, ATX up-regulation in cancer is not universal. In multiple studies, the *ENPP2* promoter region was found to be hypermethylated compared to healthy tissue, and in some cancer types (prostate, lung, breast) this correlated with decreased *ENPP2* mRNA expression, while in others, the expression of *ENPP2* was increased despite the hypermethylated promoter (Panagopoulou et al., 2021). In addition, various cellular components of the complex tumour microenvironment may differ in ATX expression and may contribute differently to the local and systemic LPA levels. In breast cancer, it was shown that ATX is, in addition to tumour cells, secreted from adjacent adipose tissue, being stimulated by pro-inflammatory cytokines, whose production is associated with tumour progression (Benesch et al., 2015a). Adipose tissue-specific *Enpp2* knockout in a mouse model, however, did not influence tumour growth, although pharmacological ATX inhibition did, pointing to ATX production by stromal cells of the tumour (Tang et al., 2023). Similarly, stromal cells, namely cancer-associated fibroblasts, macrophages and endothelial cells, have been shown to be responsible for ATX secretion in human melanoma (Matas-Rico et al., 2021). ATX expression and local and systemic LPA levels in cancer can therefore vary widely throughout the different cancer types. In most studies, however, elevated ATX and LPA are observed, regardless of the primary cellular source of ATX.

ATX and LPA signalling have been shown to influence a multitude of aspects of cancer, which could be broken down to proliferation, inflammation, migration and metastasis, but also resistance to therapy and immunity in cancer.

ATX-LPA and cell proliferation

The role of ATX in cancer cell proliferation mainly stems from LPA signalling trough LPAR1–3 receptors, which activates pro-proliferative pathways such as MAPK, PKC, PI3K/AKT, or NF-κB (Boucharaba et al., 2009; Liu et al., 2009a). LPA, present in markedly increased levels in ascites of ovarian cancer patients, is capable of inducing proliferation of ovarian cancer cells *in vitro* (Xu et al., 1995). The presence of ATX in conditioned media and LPA production had the same effect in leiomyoma cells *in vitro* (Billon-Denis et al., 2008). *SOX11* knockdown in mantle cell lymphoma cells possessed a higher secretion level of ATX, leading to increased proliferation and elevated aggressiveness in the mouse model of the disease (Conrotto et al., 2011). In acute myeloid leukaemia cells with FLT3 transcription factor gene duplication (that leads to increased ATX expression), ATX stimulated cell proliferation compared to cells without the duplication (Ortlepp et al., 2013). Conversely, inhibition of ATX has been shown to decrease cancer cell proliferation in a mouse model of breast cancer (Tang et al., 2020).

Liu et al. (2009b) brought a crucial piece of information on a direct oncogenic effect of ATX in 2009: overexpression of human ATX or one of the receptors LPARs 1–3 in transgenic mice induced inflammation and spontaneous tumour formation in the mammary gland of these animals. In the model, inflammation preceded the tumour formation.

ATX and inflammation

Inflammation is one of the landmarks of cancer (Hanahan and Weinberg, 2011). The complex process of inflammation supports tumour growth and encompasses numerous cell types and diverse processes such as immunity, fibrosis and tissue remodelling. Interactions between malignant cells and the inflammatory microenvironment play crucial roles in shaping the tumour landscape. According to current research, it seems that the interplay between ATX-LPA and inflammatory mechanisms has a major role in cancer development, namely in tumours characterized by marked ATX up-regulation.

The signalling pathways through which LPA can directly induce inflammation include transcription factors NF-κB (via activation of PKC or AKT), ATF-2 (via Rho-CDC42-p38 and JNK) c-JUN, and c-FOS (via Rho-CDC42-JNK) (see Fig. 3) (Liu et al., 2009a) in target cells. However, inflammation can also be stimulated indirectly, through transactivation of receptor tyrosine kinases such as EGFR, PDGFRβ, c-Met. Examples of such transactivation are, for instance, LPAR-dependent G-protein activation of Src kinase, which then phosphorylates EGFR, or LPAR-based activation of the MAPK pathway, which in turn leads to production of heparin-binding EGF-like growth factor, which again activates EGFR, leading to activation of transcription factors, including those mentioned above (Umata et al., 2001; Shah et al., 2005; Liu et al., 2009a). The transcription factors then elicit expression of pro-inflammatory cytokines such as CCL2, CCL3, CXCL10, ICAM1, IL-6, and IL-8 by the target cells (Magkrioti et al., 2022).

Pharmacological inhibition of ATX was shown to lead to decreased expression of genes encoding pro-inflammatory IL-1β and IL-6 (Benesch et al., 2014). On the other side, over-expression of LPA receptors increased production of the pro-inflammatory cytokines IL-6, IL-8, and VEGF in human ovarian cancer cells (Yu et al., 2008).

Interestingly, the role of ATX in inflammation seems to be augmented by a positive feedback regulation. Under standard conditions, elevated LPA levels inhibit ATX expression. However, it was demonstrated that the ATX up-regulation by pro-inflammatory cytokines (such as TNF-α, IL-1β, or IL-6) fully overcomes this negative feedback loop, leading to amplified pro-inflammatory signalling (Benesch et al., 2015b). Inhibition of ATX, on the other hand, led to a decrease of multiple inflammatory mediators in breast cancer-adjacent adipose tissue (Benesch et al., 2015a) and thyroid cancer (Benesch et al., 2015c).

Another nexus of ATX and inflammation is the production of eicosanoids. Via PKC and NF-κB, LPA stimulates expression of cyclooxygenase 2 (COX2) and inducible nitric oxide synthase (iNOS), which both participate in the production of eicosanoids, which further stimulate inflammation and contribute to the positive feedback loop of the ATX-LPA-inflammatory axis (Meng et al., 2017).

In cancer, chronic inflammation can lead to fibrosis. Cancer-associated fibrosis plays a critical role in regulating migration, invasion and metastasis (Piersma et al., 2020). In the livers of patients with hepatocellular carcinoma (HCC), the expression of ATX in the tumour correlated with the degree of liver inflammation (Wu et al., 2010). It was shown that tumour-derived LPA mediates a paracrine crosstalk between cancer cells and normal stromal fibroblasts, leading to production of ECM-generating cancer-associated fibroblasts (Mazzocca et al., 2011). Similarly, in mice, prolonged elevated ATX activity and increased LPA levels lead to transformation of hepatic stellate cells into cancer-associated fibroblasts, which produce pro-fibrotic factors including TGF-β, resulting in liver fibrosis. Deletion of ATX abrogates this process and limits development of chemically induced HCC in mice (Kaffe et al., 2017). The connecting link between LPA and fibrosis is the cytokine TGF-β, which in response to LPA activates the expression of pro-fibrotic genes (Shea and Teger et al., 2012; Li et al., 2017) via PI3K/Akt (Li et al., 2017) or RhoA (Xu et al., 2009) signalling.

ATX, migration and metastasis

The physiological role of ATX in cell motility is well established and acts through LPAR1–3 receptors and the subsequent Rho, PLC, PI3K and MAPK pathways, but also via direct interaction of ATX with integrins. Indeed, motility and migration of cancer cells are prerequisites for the tumour metastasis, and the role of ATX in this process has been clearly demonstrated.

In glioblastoma cells, where ATX is strongly up-regulated, LPA was shown to induce migration and invasion via LPAR1 signalling (Kishi et al., 2006). In agreement, over-expression of ATX was later shown to induce invasion and metastases in a transgenic mouse model of human breast cancer (Liu et al., 2009b). Conversely, inhibition of ATX function by blocking antibodies, low-molecular-weight inhibitors or *ENPP2* gene silencing suppressed migration in melanoma cells (Saunders et al., 2008; Gaetano et al., 2009). The inhibition was rescued by addition of LPA (Saunders et al., 2008). Pharmacological inhibition of ATX also decreased lung metastasis in a mouse model of breast cancer (Benesch et al., 2014).

The molecular mechanisms of ATX-mediated migration in cancer is not known; however, it may be analogical to the physiological one. For example, ATX-stimulated migration of umbilical cord blood-derived mesenchymal stem cells to wound sites was found to be driven by LPAR1/3-dependent E-cadherin reduction and cytoskeletal rearrangement via PKC/GSK3β/β-catenin and PKC/Rho (Ryu and Han, 2015). LPA-induced activation of protein kinase Akt-2 also seems to play a role, since Akt-2 knockdown abolishes cell migration in human epithelial cells (Ptaszynska et al., 2010).

Besides the individual signalling pathways, the role of ATX in the migration or metastasis can also be explained at the level of cell transformation in the process of epithelial-mesenchymal transition (EMT), which plays an important role in gaining the capability for invasion and metastasis in cancer cells of epithelial origin. Elevated ATX levels were reported during EMT (Ptaszynska et al., 2010; Dai et al., 2015). LPA, via its receptors and Arf6 signalling, promotes EMT (Hashimoto et al., 2016).

ATX, cell survival and therapy resistance

The connection between LPA and inhibition of both, intrinsic and extrinsic apoptotic pathways, is well established (Deng et al., 2003). Through the PI3K-Akt pathway, LPA down-regulates the Fas receptor (Meng et al., 2005), Fas ligand, caspase-3 (Sui et al., 2015), and caspase-8 (Kang et al., 2004). It also promotes phosphorylation-inhibition of pro-apoptotic BAD (Kang et al., 2004) and BAX, and up-regulation of anti-apoptotic BCL2 (Rusovici et al., 2007). However, the role of ATX and LPA in drug resistance of cancer cells is again pleiotropic.

The ATX-LPA axis protects cells against serum deprivation and starvation-induced apoptosis in mouse fibroblasts (Song et al., 2005), and spontaneous and staurosporine-induced apoptosis in B-cell precursor leukaemia cells (Satoh et al., 2007). In colon cancer cells and ovarian cancer cells, LPA provided protection against apoptosis induction under platinum-based drug treatment via activation of PI3K (Sun et al., 2009; Vidot et al., 2010). In breast cancer cells under taxol-induced mitotic arrest, ATX-induced LPA activated survival signals through PI3K-dependent removal of taxol from tubulin (Samadi et al., 2011). Conversely, ATX inhibition overturned resistance of breast cancer cells to taxol (Banerjee et al., 2017).

Another mechanism by which the ATX-LPA axis may contribute to drug resistance is PI3K-dependent stabilization and nuclear translocation of transcription factor Nrf2 (Venkatraman et al., 2015). This in turn leads to the expression of multiple multidrug-resistant transporters and several genes involved in oxidative stress protection. Indeed, elevated expression of Nrf2 is associated with tumour progression and poor outcomes in cancer patients (Jaramillo and Zhang, 2013; Shao et al., 2022).

In addition to the direct processes enabling cancer cell survival, ATX-LPA may contribute to a limited response to chemotherapy by contributing to desmoplasia – i.e., production of fibrotic tissue around the tumour, which physically limits the drug access to the cancer cells.

ATX, cancer and immunity

Escaping immune surveillance is another cancer landmark crucial for the development and progression of the

disease. Here, ATX acts through LPA and its receptors on lymphocytes and dendritic cells and influences their activity toward the tumour cells.

Recently, up-regulation of ATX and elevated production of LPA have been observed in PD-1 blockade-resistant tumours, where inhibition of ATX or blocking of LPAR5 restored the sensitivity to anti-PD-1 therapy (Konen et al., 2023). The mechanism most likely involved immunosuppressive regulation of cytotoxic T lymphocytes (Konen et al., 2023) owing to the ability of LPAR5 in $CD8^+$ T-cells to block TCR signalling, T-cell activation and proliferation (Oda et al., 2013). Similarly, in ATX-producing melanoma cells, LPA had an immunosuppressive effect, as it caused repulsion of tumour-infiltrating $CD8^+$ T cells through LPAR6 signalling (Matas-Rico et al., 2021). Such phenomenon is significant because it may impair cancer immunotherapy in general.

In addition to drug resistance, ATX up-regulation was documented in response to radiation therapy, and it seems to contribute to decreased sensitivity to radiotherapy. Elevated ATX together with LPA and inflammatory cytokines was observed in adipose tissue *in vitro* that underwent radiation doses comparable to radiotherapy (Meng et al., 2017). In mice, irradiation of mammary adipose tissue and breast tumours elevated plasma ATX *in vivo* (Meng et al., 2019). This "wound healing" response to radiotherapy was initiated by NF-κB activation (induced by the DNA-damage signalling via ATM, ATR and PARP-1), which stimulated ATX-LPA signalling, leading to secretion of inflammatory cytokines and increased expression of cyclooxygenase 2 (COX2). These effects together provide a positive feedback loop leading to further NF-κB activation and inflammatory response. This was suggested to impair anti-cancer treatment following initial radiotherapy (Meng et al., 2017). In agreement with that, experimental combination of radiotherapy and ATX inhibition in a mouse model of breast cancer led to increased apoptosis and lower cancer cell proliferation compared to radiotherapy alone (Tang et al., 2020). A similar effect was observed in a mouse model of glioblastoma (Bhave et al., 2013).

ATX as a biomarker

As a secreted glycoprotein, ATX can be detected in the blood plasma or serum. Elevated ATX levels in the blood of breast cancer patients enabled reliable discrimination of healthy individuals from breast cancer patients, sparking interest in ATX as a diagnostic biomarker (Shao et al., 2019). In this study, the breast cancer patients' ATX concentration in the serum was 291 ng/ml ATX, while in healthy controls only 254 ng/ml. Similarly, in a study of pancreatic cancer, the serum ATX concentration reached 393 ng/ml, while in healthy controls only 255 ng/ml (Chen et al., 2021). Elevated ATX concentrations in the ascites of ovarian cancer patients proved to indicate the presence of the disease (471 ng/ml) compared to benign ascites (191 ng/ml); however, no significant difference was found in the serum (Choi et al., 2023). In a melanoma patient study, the serum ATX concentration positively correlated with the disease progression (Kurano et al., 2018).

Although the circulating ATX levels may seem promising as a diagnostic marker, the specificity of such a test will be probably quite limited. The circulating ATX levels integrate the contributions of numerous ATX-producing tissues and reflect the multifaceted role of ATX in health and disease.

Therapeutic inhibition of ATX-LPA

Blocking ATX activity and the pleiotropic LPA signalling in cancer could be an effective way of inhibiting several cancer-related processes. Therefore, considerable effort has gone into development of low-molecular-weight ATX inhibitors. These are yet to be shown effective in cancer-oriented clinical trials.

Modified analogues of cyclic phosphatidic acid, a naturally occurring weak inhibitor of ATX, inhibited melanoma cell invasion *in vitro* and in a mouse model (Baker et al., 2006). Several different ATX inhibitors (hexachlorophene, bithionol, merbromin, and NSC 48300) suppressed migration of melanoma cells *in vitro*, and this effect was reversed by addition of LPA to the cells (Saunders et al., 2008). Boronic acid-based inhibitors were shown to inhibit the enzymatic activity of ATX (Albers et al., 2010b) and modulate LPA levels in the bloodstream in mice (Albers et al., 2010a).

However, three inhibitors deserve a more detailed note, being successfully used in numerous experimental studies: PF8380, ONO-8430506, and GLPG1690. PF8380 reduced systemic LPA levels in rats (Gierse et al., 2010). The same molecule was shown to decrease invasiveness of glioblastoma multiforme cells and enhance their radiosensitivity both *in vitro* and in mice (Bhave et al., 2013). PF8380 was also effective in a study that demonstrated the potentially oncogenic role of ATX as an active factor in liver fibrosis in chronic liver disease. Here, the inhibition of ATX was able to diminish chemically induced liver fibrosis in a mouse model (Kaffe et al., 2017).

The ATX inhibitor ONO-8430506 proved to be highly efficient in reducing serum ATX and LPA levels at low-dose oral administration in rats (Saga et al., 2014). In orthotropic mouse models of breast cancer, the combination of ONO-8430506 with doxorubicin limited ATX-LPA signalling in tumours, delayed tumour growth, and reduced tumour growth and metastasis to the lungs and liver by > 70 % (Benesch et al., 2014; Venkatraman et al., 2015). ATX inhibition by ONO-8430506 also abrogated breast cancer cell-driven secretion of inflammatory mediators and reduced tumour growth in a mouse model of breast cancer (Benesch et al., 2015a). Similarly encouraging results regarding the suppression of inflammatory mediators were obtained in a thyroid cancer model (Benesch et al., 2015c).

Ziritaxestat, formerly known as GLPG1690, is an ATX inhibitor that was shown to reduce cancer cell proliferation and improve sensitivity to radiotherapy in a

mouse model of breast cancer (Tang et al., 2020). Ziritaxestat had entered clinical trials for treatment of idiopathic pulmonary fibrosis (Desroy et al., 2017; Maher et al., 2018) and systemic sclerosis (Zulfikar et al., 2020); however, these clinical trials were later terminated.

IOA-289 is one of the most recent inhibitors. It slowed down breast tumour growth and dissemination. ATX inhibition by IOA-289 also suppressed the secretion of inflammatory cytokines and fibrosis in a mouse model of breast cancer (Deken et al., 2023). The compound has recently been shown to supress growth and migration in *in vitro* models of gastrointestinal tumours (Centonze et al., 2023). In a mouse model of pancreatic ductal adenocarcinoma cells, IOA-289 was also able to overcome resistance to TGF-β receptor inhibitor galunisertib and to nucleoside analogue gemcitabine (Pietrobono et al., 2023). IOA-289 recently entered a phase 1b trial for pancreatic cancer (https://clinicaltrials.gov/ct2/show/NCT05586516).

Two additional inhibitors are now undergoing clinical testing; however, none of these trials is aimed at cancer. BBT-877 and cudetaxestat (BLD-0409) are entering phase 2 clinical trials for idiopathic pulmonary fibrosis (https://clinicaltrials.gov/study/NCT05483907; https://clinicaltrials.gov/study/NCT05373914).

Conclusion

ATX has garnered considerable interest in the last three decades due to its pleiotropic effect in human physiology but also because of its role in cancer. The signalling network initiated by its product, LPA, is considerably complex. Even the first step – the ability of LPA to activate six different receptors – foreshadows the enormously wide and intricate network. This is further amplified or fine-tuned by numerous G proteins, not mentioning the downstream kinases and their potential crosstalk or transactivation.

The roles of ATX and LPA signalling in cancer are becoming clearly established and encompass proliferation, inflammation, migration and metastasis, but also cell survival and therapy and resistance, and immune system evasion. This clearly establishes ATX inhibition as an attractive therapeutic strategy. On the other side, the multitude of its physiological roles makes ATX as a drug target quite problematic, since an endless list of negative side effects can be envisioned. Although further research is needed to entangle the baffling network of LPA signalling, the successful use of ATX inhibitors in experimental cancer models provides a valuable infusion of optimism.

References

Albers, H. M., Dong, A., van Meeteren, L. A. et al. (2010a) Boronic acid-based inhibitor of autotaxin reveals rapid turnover of LPA in the circulation. *Proc. Natl. Acad. Sci. U. S. A.* **107**, 7257-7262.

Albers, H. M., van Meeteren, L. A., Egan, D. A. et al. (2010b) Discovery and optimization of boronic acid based inhibitors of autotaxin. *J. Med. Chem.* **53**, 4958-4967.

Anliker, B., Chun, J. (2004) Cell surface receptors in lysophospholipid signaling. *Semin. Cell Dev. Biol.* **15**, 457-465.

Aoki, J., Taira, A., Takanezawa, Y. et al. (2002) Serum lysophosphatidic acid is produced through diverse phospholipase pathways. *J. Biol. Chem.* **277**, 48737-48744.

Argaud, D., Boulanger, M. C., Chignon, A. et al. (2019) Enhancer-mediated enrichment of interacting JMJD3-DDX21 to ENPP2 locus prevents R-loop formation and promotes transcription. *Nucleic Acids Res.* **47**, 8424-8438.

Azare, J., Doane, A., Leslie, K. et al. (2011) Stat3 mediates expression of autotaxin in breast cancer. *PloS One* **6**, e27851.

Bai, Z., Cai, L., Umemoto, E. et al. (2013) Constitutive lymphocyte transmigration across the basal lamina of high endothelial venules is regulated by the autotaxin/lysophosphatidic acid axis. *J. Immunol.* **190**, 2036-2048.

Balazs, L., Okolicany, J., Ferrebee, M. et al. (2000) Topical application of LPA accelerates wound healing. *Ann. N. Y. Acad. Sci.* **905**, 270-273.

Baker, D. L., Fujiwara, Y., Pigg, K. R. et al. (2006) Carba analogs of cyclic phosphatidic acid are selective inhibitors of autotaxin and cancer cell invasion and metastasis. *J. Biol. Chem.* **281**, 22786-22793.

Banerjee, S., Norman, D. D., Lee, S. C. et al. (2017) Highly potent non-carboxylic acid autotaxin inhibitors reduce melanoma metastasis and chemotherapeutic resistance of breast cancer stem cells. *J. Med. Chem.* **60**, 1309-1324.

Barbayianni, E., Kaffe, E., Aidinis, V. et al. (2015) Autotaxin, a secreted lysophospholipase D, as a promising therapeutic target in chronic inflammation and cancer. *Prog. Lipid Res.* **58**, 76-96.

Benesch, M. G., Tang, X., Maeda, T. et al. (2014) Inhibition of autotaxin delays breast tumor growth and lung metastasis in mice. *FASEB J.* **28**, 2655-2666.

Benesch, M. G., Tang, X., Dewald, J. et al. (2015a) Tumor-induced inflammation in mammary adipose tissue stimulates a vicious cycle of autotaxin expression and breast cancer progression. *FASEB J.* **29**, 3990-4000.

Benesch, M. G., Zhao, Y. Y., Curtis, J. M. et al. (2015b) Regulation of autotaxin expression and secretion by lysophosphatidate and sphingosine 1-phosphate. *J. Lipid Res.* **56**, 1134-1144.

Benesch, M. G., Ko, Y. M., Tang, X. et al. (2015c) Autotaxin is an inflammatory mediator and therapeutic target in thyroid cancer. *Endocr. Relat. Cancer* **22**, 593-607.

Bhave, S. R., Dadey, D. Y., Karvas, R. M. et al. (2013) Autotaxin inhibition with PF-8380 enhances the radiosensitivity of human and murine glioblastoma cell lines. *Front. Oncol.* **3**, 236.

Billon-Denis, E., Tanfin, Z., Robin, P. (2008) Role of lysophosphatidic acid in the regulation of uterine leiomyoma cell proliferation by phospholipase D and autotaxin. *J. Lipid Res.* **49**, 295-307.

Boucharaba, A., Guillet, B., Menaa, F. et al. (2009) Bioactive lipids lysophosphatidic acid and sphingosine 1-phosphate mediate breast cancer cell biological functions through distinct mechanisms. *Oncol. Res.* **18**, 173-184.

Brindley, D. N., Lin, F. T., Tigyi, G. J. (2013) Role of the autotaxin-lysophosphatidate axis in cancer resistance to chemotherapy and radiotherapy. *Biochim. Biophys. Acta* **1831**, 74-85.

Cao, P., Walker, N. M., Braeuer, R. R. et al. (2020) Loss of FOXF1 expression promotes human lung-resident mesenchymal stromal cell migration via ATX/LPA/LPA1 signaling axis. *Sci. Rep.* **10**, 21231.

Centonze, M., Di Conza, G., Lahn, M. et al. (2023) Autotaxin inhibitor IOA-289 reduces gastrointestinal cancer progression in preclinical models. *J. Exp. Clin. Cancer Res.* **42**, 197.

Chabaud, S., Marcoux, T. L., Deschênes-Rompré, M. P. et al. (2015) Lysophosphatidic acid enhances collagen deposition and matrix thickening in engineered tissue. *J. Tissue Eng. Regen. Med.* **9**, E65-E75.

Chen, M., O'Connor, K. L. (2005) Integrin α6β4 promotes expression of autotaxin/ENPP2 autocrine motility factor in breast carcinoma cells. *Oncogene* **24**, 5125-5130.

Chen, J., Li, H., Xu, W. et al. (2021) Evaluation of serum ATX and LPA as potential diagnostic biomarkers in patients with pancreatic cancer. *BMC Gastroenterol.* **21**, 58.

Choi, J. W., Herr, D. R., Noguchi, K. et al. (2010) LPA receptors: subtypes and biological actions. *Annu. Rev. Pharmacol. Toxicol.* **50**, 157-186.

Choi, J. A., Kim, H., Kwon, H. et al. (2023) Ascitic autotaxin as a potential prognostic, diagnostic, and therapeutic target for epithelial ovarian cancer. *Br. J. Cancer* **129**, 1184-1194.

Clair, T., Lee, H. Y., Liotta, L. A. et al. (1997) Autotaxin is an exoenzyme possessing 5'-nucleotide phosphodiesterase/ATP pyrophosphatase and ATPase activities. *J. Biol. Chem.* **272**, 996-1001.

Conrotto, P., Andréasson, U., Kuci, V. et al. (2011) Knockdown of SOX11 induces autotaxin-dependent increase in proliferation in vitro and more aggressive tumors in vivo. *Mol. Oncol.* **5**, 527-537.

Cooper, A. B., Wu, J., Lu, D. et al. (2007) Is autotaxin (ENPP2) the link between hepatitis C and hepatocellular cancer? *J. Gastrointest. Surg.* **11**, 1628-1635.

Dai, W., Wang, F., He, L. et al. (2015) Genistein inhibits hepatocellular carcinoma cell migration by reversing the epithelial-mesenchymal transition: partial mediation by the transcription factor NFAT1. *Mol. Carcinog.* **54**, 301-311.

Deken, M. A., Niewola-Staszkowska, K., Peyruchaud, O. et al. (2023) Characterization and translational development of IOA-289, a novel autotaxin inhibitor for the treatment of solid tumors. *Immunooncol. Technol.* **18**, 100384.

Deng, W., Wang, D. A., Gosmanova, E. et al. (2003) LPA protects intestinal epithelial cells from apoptosis by inhibiting the mitochondrial pathway. *Am. J. Physiol. Gastrointest. Liver Physiol.* **284**, G821-G829.

Desroy, N., Housseman, C., Bock, X. et al. (2017) Discovery of 2-[[2-ethyl-6-[4-[2-(3-hydroxyazetidin-1-yl)-2-oxoethyl] piperazin-1-yl]-8-methylimidazo[1,2-a]pyridin-3-yl] methylamino]-4-(4-fluorophenyl)thiazole-5-carbonitrile (GLPG1690), a first-in-class autotaxin inhibitor undergoing clinical evaluation for the treatment of idiopathic pulmonary fibrosis. *J. Med. Chem.* **60**, 3580-3590.

Farquhar, M. J., Humphreys, I. S., Rudge, S. A. et al. (2017) Autotaxin-lysophosphatidic acid receptor signalling regulates hepatitis C virus replication. *J. Hepatol.* **66**, 919-929.

Ferry, G., Giganti, A., Cogé, F. et al. (2007) Functional invalidation of the autotaxin gene by a single amino acid mutation in mouse is lethal. *FEBS Lett.* **581**, 3572-3578.

Federico, L., Jeong, K. J., Vellano, C. P. et al. (2016) Autotaxin, a lysophospholipase D with pleomorphic effects in oncogenesis and cancer progression. *J. Lipid Res.* **57**, 25-35.

Fotopoulou, S., Oikonomou, N., Grigorieva, E. et al. (2010) ATX expression and LPA signalling are vital for the development of the nervous system. *Dev. Biol.* **339**, 451-464.

Fulkerson, Z., Wu, T., Sunkara, M. et al. (2011) Binding of autotaxin to integrins localizes lysophosphatidic acid production to platelets and mammalian cells. *J. Biol. Chem.* **286**, 34654-34663.

Gaetano, C. G., Samadi, N., Tomsig, J. L. et al. (2009) Inhibition of autotaxin production or activity blocks lysophosphatidylcholine-induced migration of human breast cancer and melanoma cells. *Mol. Carcinog.* **48**, 801-809.

Gao, J., Aksoy, B. A., Dogrusoz, U. et al. (2013) Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. *Sci. Signal.* **6**, pl1.

Georas S. N. (2009) Lysophosphatidic acid and autotaxin: emerging roles in innate and adaptive immunity. *Immunol. Res.* **45**, 229-238.

Gierse, J., Thorarensen, A., Beltey, K. et al. (2010) A novel autotaxin inhibitor reduces lysophosphatidic acid levels in plasma and the site of inflammation. *J. Pharmacol. Exp. Ther.* **334**, 310-317.

Giganti, A., Rodriguez, M., Fould, B. et al. (2008) Murine and human autotaxin α, β, and γ isoforms: gene organization, tissue distribution, and biochemical characterization. *J. Biol. Chem.* **283**, 7776-7789.

Gijsbers, R., Ceulemans, H., Stalmans, W. et al. (2001) Structural and catalytic similarities between nucleotide pyrophosphatases/phosphodiesterases and alkaline phosphatases. *J. Biol. Chem.* **276**, 1361-1368.

Goding, J. W., Grobben, B., Slegers, H. (2003) Physiological and pathophysiological functions of the ecto-nucleotide pyrophosphatase/phosphodiesterase family. *Biochim. Biophys. Acta* **1638**, 1-19.

Goetzl, E. J., An, S. (1999) A subfamily of G protein-coupled cellular receptors for lysophospholipids and lysosphingolipids. *Adv. Exp. Med. Biol.* **469**, 259-264.

Hanahan, D., Weinberg, R. A. (2011) Hallmarks of cancer: the next generation. *Cell* **144**, 646-674.

Hashimoto, T., Okudaira, S., Igarashi, K. et al. (2012) Identification and biochemical characterization of a novel autotaxin isoform, ATXδ, with a four-amino acid deletion. *J. Biochem.* **151**, 89-97.

Hashimoto, S., Mikami, S., Sugino, H. et al. (2016) Lysophosphatidic acid activates Arf6 to promote the mesenchymal malignancy of renal cancer. *Nat. Commun.* **7**, 10656.

Hausmann, J., Kamtekar, S., Christodoulou, E. et al. (2011) Structural basis of substrate discrimination and integrin binding by autotaxin. *Nat. Struct. Mol. Biol.* **18**, 198-204.

He, L., Yang, Y., Chen, J. et al. (2021) Transcriptional activation of ENPP2 by FoxO4 protects cardiomyocytes from doxorubicin-induced toxicity. *Mol. Med. Rep.* **24**, 668.

Hoelzinger, D. B., Mariani, L., Weis, J. et al. (2005) Gene expression profile of glioblastoma multiforme invasive phenotype points to new therapeutic targets. *Neoplasia* **7**, 7-16.

Houben, A. J., van Wijk, X. M., van Meeteren, L. A. et al. (2013) The polybasic insertion in autotaxin α confers specific binding to heparin and cell surface heparan sulfate proteoglycans. *J. Biol. Chem.* **288**, 510-519.

Ishii, S., Hirane, M., Fukushima, K. et al. (2015) Diverse effects of LPA4, LPA5 and LPA6 on the activation of tumor progression in pancreatic cancer cells. *Biochem. Biophys. Res. Commun.* **461**, 59-64.

Jaramillo, M. C., Zhang, D. D. (2013) The emerging role of the Nrf2-Keap1 signaling pathway in cancer. *Genes Dev.* **27**, 2179-2191.

Jansen, S., Stefan, C., Creemers, J. W. et al. (2005) Proteolytic maturation and activation of autotaxin (NPP2), a secreted metastasis-enhancing lysophospholipase D. *J. Cell Sci.* **118(Pt 14)**, 3081-3089.

Jansen, S., Callewaert, N., Dewerte, I. et al. (2007) An essential oligomannosidic glycan chain in the catalytic domain of autotaxin, a secreted lysophospholipase-D. *J. Biol. Chem.* **282**, 11084-11091.

Jansen, S., Andries, M., Derua, R. et al. (2009) Domain interplay mediated by an essential disulfide linkage is critical for the activity and secretion of the metastasis-promoting enzyme autotaxin. *J. Biol. Chem.* **284**, 14296-14302.

Jongsma, M., Matas-Rico, E., Rzadkowski, A. et al. (2011) LPA is a chemorepellent for B16 melanoma cells: action through the cAMP-elevating LPA5 receptor. *PloS One* **6**, e29260.

Jose, A., Kienesberger, P. C. (2021) Autotaxin-LPA-LPP3 axis in energy metabolism and metabolic disease. *Int. J. Mol Sci.* **22**, 9575.

Kaffe, E., Katsifa, A., Xylourgidis, N. et al. (2017) Hepatocyte autotaxin expression promotes liver fibrosis and cancer. *Hepatology* **65**, 1369-1383.

Kanda, H., Newton, R., Klein, R. et al. (2008) Autotaxin, an ectoenzyme that produces lysophosphatidic acid, promotes the entry of lymphocytes into secondary lymphoid organs. *Nat. Immunol.* **9**, 415-423.

Kang, Y. C., Kim, K. M., Lee, K. S. et al. (2004) Serum bioactive lysophospholipids prevent TRAIL-induced apoptosis via PI3K/Akt-dependent cFLIP expression and Bad phosphorylation. *Cell Death Differ.* **11**, 1287-1298.

Katsifa, A., Kaffe, E., Nikolaidou-Katsaridou, N. et al. (2015) The bulk of autotaxin activity is dispensable for adult mouse life. *PloS One* **10**, e0143083.

Kehlen, A., Englert, N., Seifert, A. et al. (2004) Expression, regulation and function of autotaxin in thyroid carcinomas. *Int. J. Cancer* **109**, 833-838.

Kishi, Y., Okudaira, S., Tanaka, M. et al. (2006) Autotaxin is overexpressed in glioblastoma multiforme and contributes to cell motility of glioblastoma by converting lysophosphatidylcholine to lysophosphatidic acid. *J. Biol. Chem.* **281**, 17492-17500.

Knowlden, S., Georas, S. N. (2014) The autotaxin-LPA axis emerges as a novel regulator of lymphocyte homing and inflammation. *J. Immunol.* **192**, 851-857.

Konen, J. M., Rodriguez, B. L., Wu, H. et al. (2023) Autotaxin suppresses cytotoxic T cells via LPAR5 to promote anti-PD-1 resistance in non-small cell lung cancer. *J. Clin. Invest.* **133**, e163128.

Kurano, M., Miyagaki, T., Miyagawa, T. et al. (2018) Association between serum autotaxin or phosphatidylserine-specific phospholipase A1 levels and melanoma. *J. Dermatol.* **45**, 571-579.

Leblanc, R., Sahay, D., Houssin, A. et al. (2018) Autotaxin-β interaction with the cell surface via syndecan-4 impacts on cancer cell proliferation and metastasis. *Oncotarget* **9**, 33170-33185.

Lee, H. Y., Murata, J., Clair, T. et al. (1996) Cloning, chromosomal localization, and tissue expression of autotaxin from human teratocarcinoma cells. *Biochem. Biophys. Res. Commun.* **218**, 714-719.

Lee, J., Jung, I. D., Nam, S. W. et al. (2001) Enzymatic activation of autotaxin by divalent cations without EF-hand loop region involvement. *Biochem. Pharmacol.* **62**, 219-224.

Lee, Z., Cheng, C. T., Zhang, H. et al. (2008) Role of LPA4/p2y9/GPR23 in negative regulation of cell motility. *Mol. Biol. Cell* **19**, 5435-5445.

Li, S., Wang, B., Xu, Y. et al. (2011) Autotaxin is induced by TSA through HDAC3 and HDAC7 inhibition and antagonizes the TSA-induced cell apoptosis. *Mol. Cancer* **10**, 18.

Li, H., Yue, R., Wei, B. et al. (2014) Lysophosphatidic acid acts as a nutrient-derived developmental cue to regulate early hematopoiesis. *EMBO J.* **33**, 1383-1396.

Li, H. Y., Oh, Y. S., Choi, J. W. et al. (2017) Blocking lysophosphatidic acid receptor 1 signaling inhibits diabetic nephropathy in db/db mice. *Kidney Int.* **91**, 1362-1373.

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

Lin, K. H., Lee, S. C., Dacheux, M. A. et al. (2023) E2F7 drives autotaxin/Enpp2 transcription via chromosome looping: repression by p53 in murine but not in human carcinomas. *FASEB J.* **37**, e23058.

Liu, S., Murph, M., Panupinthu, N. et al. (2009a) ATX-LPA receptor axis in inflammation and cancer. *Cell Cycle* **8**, 3695-3701.

Liu, S., Umezu-Goto, M., Murph, M. et al. (2009b) Expression of autotaxin and lysophosphatidic acid receptors increases mammary tumorigenesis, invasion, and metastases. *Cancer Cell* **15**, 539-550.

Magkrioti, C., Antonopoulou, G., Fanidis, D. et al. (2022) Lysophosphatidic acid is a proinflammatory stimulus of renal tubular epithelial cells. *Int. J. Mol. Sci.* **23**, 7452.

Maher, T. M., van der Aar, E. M., van de Steen, O. et al. (2018) Safety, tolerability, pharmacokinetics, and pharmacodynamics of GLPG1690, a novel autotaxin inhibitor, to treat idiopathic pulmonary fibrosis (FLORA): a phase 2a randomised placebo-controlled trial. *Lancet Respir. Med.* **6**, 627-635.

Matas-Rico, E., Frijlink, E., van der Haar Àvila, I. et al. (2021) Autotaxin impedes anti-tumor immunity by suppressing chemotaxis and tumor infiltration of $CD8^+$ T cells. *Cell Rep.* **37**, 110013.

Masuda, A., Nakamura, K., Izutsu, K. et al. (2008) Serum autotaxin measurement in haematological malignancies: a promising marker for follicular lymphoma. *Br. J. Haematol.* **143**, 60-70.

Mazzocca, A., Dituri, F., Lupo, L. et al. (2011) Tumor-secreted lysophostatidic acid accelerates hepatocellular carcinoma progression by promoting differentiation of peritumoral fibroblasts in myofibroblasts. *Hepatology* **54**, 920-930.

Mazzocca, A., Schönauer, L. M., De Nola, R. et al. (2018) Autotaxin is a novel molecular identifier of type I endometrial cancer. *Med. Oncol.* **35**, 157.

Meng, Y., Kang, S., Fishman, D. A. (2005) Lysophosphatidic acid inhibits anti-Fas-mediated apoptosis enhanced by actin depolymerization in epithelial ovarian cancer. *FEBS Lett.* **579**, 1311-1319.

Meng, G., Tang, X., Yang, Z. et al. (2017) Implications for breast cancer treatment from increased autotaxin production in adipose tissue after radiotherapy. *FASEB J.* **31**, 4064-4077.

Meng, G., Tang, X., Yang, Z. et al. (2019) Dexamethasone decreases the autotaxin-lysophosphatidate-inflammatory axis in adipose tissue: implications for the metabolic syndrome and breast cancer. *FASEB J.* **33**, 1899-1910.

Moolenaar, W. H., Perrakis, A. (2011) Insights into autotaxin: how to produce and present a lipid mediator. *Nat. Rev. Mol. Cell Biol.* **12**, 674-679.

Murata, J., Lee, H. Y., Clair, T. et al. (1994) cDNA cloning of the human tumor motility-stimulating protein, autotaxin, reveals a homology with phosphodiesterases. *J. Biol. Chem.* **269**, 30479-30484.

Murph, M. M. (2019) MicroRNA regulation of the autotaxin-lysophosphatidic acid signaling axis. *Cancers (Basel)* **11**, 1369.

Nakai, Y., Ikeda, H., Nakamura, K. et al. (2011) Specific increase in serum autotaxin activity in patients with pancreatic cancer. *Clin. Biochem.* **44**, 576-581.

Nishimasu, H., Okudaira, S., Hama, K. et al. (2011) Crystal structure of autotaxin and insight into GPCR activation by lipid mediators. *Nat. Struct. Mol. Biol.* **18**, 205-212.

Nishimura, S., Nagasaki, M., Okudaira, S. et al. (2014) ENPP2 contributes to adipose tissue expansion and insulin resistance in diet-induced obesity. *Diabetes* **63**, 4154-4164.

Nouh, M. A., Wu, X. X., Okazoe, H. et al. (2009) Expression of autotaxin and acylglycerol kinase in prostate cancer: association with cancer development and progression. *Cancer Sci.* **100**, 1631-1638.

Oda, S. K., Strauch, P., Fujiwara, Y. et al. (2013) Lysophosphatidic acid inhibits CD8 T cell activation and control of tumor progression. *Cancer Immunol. Res.* **1**, 245-255.

Ortlepp, C., Steudel, C., Heiderich, C. et al. (2013) Autotaxin is expressed in FLT3-ITD positive acute myeloid leukemia and hematopoietic stem cells and promotes cell migration and proliferation. *Exp. Hematol.* **41**, 444-461.e4.

Panagopoulou, M., Fanidis, D., Aidinis, V. et al. (2021) *ENPP2* methylation in health and cancer. *Int. J. Mol. Sci.* **22**, 11958.

Panagopoulou, M., Drosouni, A., Fanidis, D. et al. (2022) *ENPP2* promoter methylation correlates with decreased gene expression in breast cancer: implementation as a liquid biopsy biomarker. *Int. J. Mol. Sci*. **23**, 3717.

Park, S. Y., Jeong, K. J., Panupinthu, N. et al. (2011) Lysophosphatidic acid augments human hepatocellular carcinoma cell invasion through LPA1 receptor and MMP-9 expression. *Oncogene* **30**, 1351-1359.

Patterson, A. D., Maurhofer, O., Beyoglu, D. et al. (2011) Aberrant lipid metabolism in hepatocellular carcinoma revealed by plasma metabolomics and lipid profiling. *Cancer Res.* **71**, 6590-6600.

Piersma, B., Hayward, M. K., Weaver, V. M. (2020) Fibrosis and cancer: a strained relationship. *Biochim. Biophys. Acta Rev. Cancer* **1873**, 188356.

Pietrobono, S., Sabbadini, F., Bertolini, M. et al. (2023) Autotaxin secretion is a stromal mechanism of adaptive resistance to TGFβ inhibition in pancreatic ductal adenocarcinoma. *Cancer Res.* Online ahead. https://doi.org/10.1158/0008-5472.CAN-23-0104

Pradère, J. P., Tarnus, E., Grès, S. et al. (2007) Secretion and lysophospholipase D activity of autotaxin by adipocytes are controlled by N-glycosylation and signal peptidase. *Biochim. Biophys. Acta* **1771**, 93-102.

Ptaszynska, M. M., Pendrak, M. L., Stracke, M. L. et al. (2010) Autotaxin signaling via lysophosphatidic acid receptors contributes to vascular endothelial growth factor-induced endothelial cell migration. *Mol. Cancer Res.* **8**, 309-321.

Qu, M., Long, Y., Wang, Y. et al. (2023) Hypoxia increases ATX expression by histone crotonylation in a HIF-2α-dependent manner. *Int. J. Mol. Sci.* **24**, 7031.

Ray, R., Rai, V. (2017) Lysophosphatidic acid converts monocytes into macrophages in both mice and humans. *Blood* **129**, 1177-1183.

Rivera-Lopez, C. M., Tucker, A. L., Lynch, K. R. (2008) Lysophosphatidic acid (LPA) and angiogenesis. *Angiogenesis* **11**, 301-310.

Rusovici, R., Ghaleb, A., Shim, H. et al. (2007) Lysophosphatidic acid prevents apoptosis of Caco-2 colon cancer cells via activation of mitogen-activated protein kinase and phosphorylation of Bad. *Biochim. Biophys. Acta* **1770**, 1194-1203.

Ryu, J. M., Han, H. J. (2015) Autotaxin-LPA axis regulates hMSC migration by adherent junction disruption and cytoskeletal rearrangement via LPAR1/3-dependent PKC/GSK3β/β-catenin and PKC/Rho GTPase pathways. *Stem Cells* **33**, 819-832.

Saga, H., Ohhata, A., Hayashi, A. et al. (2014) A novel highly potent autotaxin/ENPP2 inhibitor produces prolonged decreases in plasma lysophosphatidic acid formation in vivo and regulates urethral tension. *PloS One* **9**, e93230.

Sah, J. P., Hao, N. T. T., Han, X. et al. (2020) Ectonucleotide pyrophosphatase 2 (ENPP2) plays a crucial role in myogenic differentiation through the regulation by WNT/β-Catenin signaling. *Int. J. Biochem. Cell Biol.* **118**, 105661.

Samadi, N., Bekele, R. T., Goping, I. S. et al. (2011) Lysophosphatidate induces chemo-resistance by releasing breast cancer cells from taxol-induced mitotic arrest. *PloS One* **6**, e20608.

Satoh, Y., Ohkawa, R., Nakamura, K. et al. (2007) Lysophosphatidic acid protection against apoptosis in the human pre-B-cell line Nalm-6. *Eur. J. Haematol.* **78**, 510-517.

Saunders, L. P., Ouellette, A., Bandle, R. et al. (2008) Identification of small-molecule inhibitors of autotaxin that inhibit melanoma cell migration and invasion. *Mol. Cancer Ther.* **7**, 3352-3362.

Saunders, L. P., Cao, W., Chang, W. C. et al. (2011) Kinetic analysis of autotaxin reveals substrate-specific catalytic pathways and a mechanism for lysophosphatidic acid distribution. *J. Biol. Chem.* **286**, 30130-30141.

Sevastou, I., Kaffe, E., Mouratis, M. A. et al. (2013) Lysoglycerophospholipids in chronic inflammatory disorders: the PLA(2)/LPC and ATX/LPA axes. *Biochim. Biophys. Acta* **1831**, 42-60.

Shah, B. H., Baukal, A. J., Shah, F. B. et al. (2005) Mechanisms of extracellularly regulated kinases 1/2 activation in adrenal glomerulosa cells by lysophosphatidic acid and epidermal growth factor. *Mol. Endocrinol.* **19**, 2535-2548.

Shao, Y., Yu, Y., He, Y. et al. (2019) Serum ATX as a novel biomarker for breast cancer. *Medicine (Baltimore)* **98**, e14973.

Shao, Z. C., Zhu, B. H., Huang, A. F. et al. (2022) Docosahexaenoic acid reverses epithelial-mesenchymal transition and drug resistance by impairing the PI3K/AKT/Nrf2/GPX4 signalling pathway in docetaxel-resistant PC3 prostate cancer cells. *Folia Biol. (Praha)* **68**, 59-71.

Shea, B. S., Tager, A. M. (2012) Role of the lysophospholipid mediators lysophosphatidic acid and sphingosine 1-phosphate in lung fibrosis. *Proc. Am. Thorac. Soc.* **9**, 102-110.

Shida, D., Watanabe, T., Aoki, J. et al. (2004) Aberrant expression of lysophosphatidic acid (LPA) receptors in human colorectal cancer. *Lab. Invest.* **84**, 1352-1362.

Sioletic, S., Czaplinski, J., Hu, L. et al. (2014) c-Jun promotes cell migration and drives expression of the motility factor ENPP2 in soft tissue sarcomas. *J. Pathol.* **234**, 190-202.

Song, J., Clair, T., Noh, J. H. et al. (2005) Autotaxin (lysoPLD/NPP2) protects fibroblasts from apoptosis through its enzymatic product, lysophosphatidic acid, utilizing albumin-bound substrate. *Biochem. Biophys. Res. Commun.* **337**, 967-975.

Stassar, M. J., Devitt, G., Brosius, M. et al. (2001) Identification of human renal cell carcinoma associated genes by suppression subtractive hybridization. *Br. J. Cancer* **85**, 1372-1382.

Stefan, C., Jansen, S., Bollen, M. (2005) NPP-type ectophosphodiesterases: unity in diversity. *Trends Biochem. Sci.* **30**, 542-550.

Stracke, M. L., Krutzsch, H. C., Unsworth, E. J. et al. (1992) Identification, purification, and partial sequence analysis of autotaxin, a novel motility-stimulating protein. *J. Biol. Chem.* **267**, 2524-2529.

Sui, Y., Yang, Y., Wang, J. et al. (2015) Lysophosphatidic acid inhibits apoptosis induced by cisplatin in cervical cancer cells. *Biomed Res. Int.* **2015**, 598386.

Sun, H., Ren, J., Zhu, Q. et al. (2009) Effects of lysophosphatidic acid on human colon cancer cells and its mechanisms of action. *World J. Gastroenterol.* **15**, 4547-4555.

Sun, S., Zhang, X., Lyu, L. et al. (2016) Autotaxin expression is regulated at the post-transcriptional level by the RNA-binding proteins HuR and AUF1. *J. Biol. Chem.* **291**, 25823-25836.

Sun, S., Wang, R., Song, J. et al. (2017) Blocking gp130 signaling suppresses autotaxin expression in adipocytes and improves insulin sensitivity in diet-induced obesity. *J. Lipid Res.* **58**, 2102-2113.

Takahashi, K., Fukushima, K., Onishi, Y. et al. (2017) Lysophosphatidic acid (LPA) signaling via LPA_4 and LPA_6 negatively regulates cell motile activities of colon cancer cells. *Biochem. Biophys. Res. Commun.* **483**, 652-657.

Takeda, A., Kobayashi, D., Aoi, K. et al. (2016) Fibroblastic reticular cell-derived lysophosphatidic acid regulates confined intranodal T-cell motility. *eLife* **5**, e10561.

Tanaka, M., Okudaira, S., Kishi, Y. et al. (2006) Autotaxin stabilizes blood vessels and is required for embryonic vasculature by producing lysophosphatidic acid. *J. Biol. Chem.* **281**, 25822-25830.

Tang, X., Benesch, M. G., Brindley, D. N. (2015) Lipid phosphate phosphatases and their roles in mammalian physiology and pathology. *J. Lipid Res.* **56**, 2048-2060.

Tang, X., Wuest, M., Benesch, M. G. K. et al. (2020) Inhibition of autotaxin with GLPG1690 increases the efficacy of radiotherapy and chemotherapy in a mouse model of breast cancer. *Mol. Cancer Ther.* **19**, 63-74.

Tang, X., Morris, A. J., Deken, M. A. et al. (2023) Autotaxin inhibition with IOA-289 decreases breast tumor growth in mice whereas knockout of autotaxin in adipocytes does not. *Cancers (Basel)* **15**, 2937.

Tigyi, G. (2010) Aiming drug discovery at lysophosphatidic acid targets. *Br. J. Pharmacol.* **161**, 241-270.

Tokumura, A., Majima, E., Kariya, Y. et al. (2002) Identification of human plasma lysophospholipase D, a lysophosphatidic acid-producing enzyme, as autotaxin, a multifunctional phosphodiesterase. *J. Biol. Chem.* **277**, 39436-39442.

Tokumura, A., Kume, T., Fukuzawa, K. et al. (2007) Peritoneal fluids from patients with certain gynecologic tumor contain elevated levels of bioactive lysophospholipase D activity. *Life Sci.* **80**, 1641-1649.

Umata, T., Hirata, M., Takahashi, T. et al. (2001) A dual signaling cascade that regulates the ectodomain shedding of heparin-binding epidermal growth factor-like growth factor. *J. Biol. Chem.* **276**, 30475-30482.

Umezu-Goto, M., Kishi, Y., Taira, A. et al. (2002) Autotaxin has lysophospholipase D activity leading to tumor cell growth and motility by lysophosphatidic acid production. *J. Cell Biol*. **158**, 227-233.

van Corven, E. J., van Rijswijk, A., Jalink, K. et al. (1992) Mitogenic action of lysophosphatidic acid and phosphatidic acid on fibroblasts. Dependence on acyl-chain length and inhibition by suramin. *Biochem. J.* **281(Pt 1)**, 163-169.

van Meeteren, L. A., Ruurs, P., Stortelers, C. et al. (2006) Autotaxin, a secreted lysophospholipase D, is essential for blood vessel formation during development. *Mol. Cell. Biol.* **26**, 5015-5022.

Venkatraman, G., Benesch, M. G., Tang, X. et al. (2015) Lysophosphatidate signaling stabilizes Nrf2 and increases the expression of genes involved in drug resistance and oxidative stress responses: implications for cancer treatment. *FASEB J.* **29**, 772-785.

Vidot, S., Witham, J., Agarwal, R. et al. (2010) Autotaxin delays apoptosis induced by carboplatin in ovarian cancer cells. *Cell. Signal.* **22**, 926-935.

Vít, O., Talacko, P., Musil, Z. et al. (2023) Identification of potential molecular targets for the treatment of cluster 1 human pheochromocytoma and paraganglioma via com-

prehensive proteomic characterization. *Clin. Proteomics* **20**, 39.

Wang, Y., Lyu, L., Zhang, X. et al. (2019) Autotaxin is a novel target of microRNA-101-3p. *FEBS Open Bio* **9**, 707-716.

Williams, T. M., Williams, M. E., Kuick, R. et al. (2005) Candidate downstream regulated genes of HOX group 13 transcription factors with and without monomeric DNA binding capability. *Dev. Biol.* **279**, 462-480.

Wu, J. M., Xu, Y., Skill, N. J. et al. (2010) Autotaxin expression and its connection with the TNF-alpha-NF-κB axis in human hepatocellular carcinoma. *Mol. Cancer* **9**, 71.

Wu, T., Kooi, C. V., Shah, P. et al. (2014) Integrin-mediated cell surface recruitment of autotaxin promotes persistent directional cell migration. *FASEB J.* **28**, 861-870.

Xie, D., Yu, S., Li, L. et al. (2020) The FOXM1/ATX signaling contributes to pancreatic cancer development. *Am. J. Transl. Res.* **12**, 4478-4487.

Xu, Y., Fang, X. J., Casey, G. et al. (1995) Lysophospholipids activate ovarian and breast cancer cells. *Biochem J.* **309(Pt 3)**, 933-940.

Xu, M. Y., Porte, J., Knox, A. J. et al. (2009) Lysophosphatidic acid induces αvβ6 integrin-mediated TGF-β activation via the LPA2 receptor and the small G protein $G\alpha_q$. *Am. J. Pathol.* **174**, 1264-1279.

Xu, A., Khan, A. K.., Chen, F. et al. (2016) Overexpression of autotaxin is associated with human renal cell carcinoma and bladder carcinoma and their progression. *Med. Oncol.* **33**, 131.

Xu, X., Zhang, Y., Zhang, J. et al. (2020) NSun2 promotes cell migration through methylating autotaxin mRNA. *J. Biol. Chem.* **295**, 18134-18147.

Yang, Y., Mou, L.-J., Liu, N. et al. (1999) Autotaxin expression in non-small-cell lung cancer. *Am. J. Respir. Cell Mol. Biol.* **21**, 216-222.

Yu, S., Murph, M. M., Lu, Y. et al. (2008) Lysophosphatidic acid receptors determine tumorigenicity and aggressiveness of ovarian cancer cells. *J. Natl. Cancer Inst.* **100**, 1630-1642.

Yung, Y. C., Stoddard, N. C., Chun, J. (2014) LPA receptor signaling: pharmacology, physiology, and pathophysiology. *J. Lipid Res.* **55**, 1192-1214.

Zhang, Y., Chen, Y. C., Krummel, M. F. et al. (2012) Autotaxin through lysophosphatidic acid stimulates polarization, motility, and transendothelial migration of naive T cells. *J. Immunol.* **189**, 3914-3924.

Zeng, R., Li, B., Huang, J. et al. (2017) Lysophosphatidic acid is a biomarker for peritoneal carcinomatosis of gastric cancer and correlates with poor prognosis. *Genet. Test. Mol. Biomarkers* **21**, 641-648.

Zuckerman, V., Sokolov, E., Swet, J. H. et al. (2016) Expression and function of lysophosphatidic acid receptors (LPARs) 1 and 3 in human hepatic cancer progenitor cells. *Oncotarget* **7**, 2951-2967.

Zulfikar, S., Mulholland, S., Adamali, H. et al. (2020) Inhibitors of the autotaxin-lysophosphatidic acid axis and their potential in the treatment of interstitial lung disease: current perspectives. *Clin. Pharmacol.* **12**, 97-108.