Biology and function of the autotaxin/lysophosphatidic acid axis in cancer (Review)

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Abstract. Autotaxin (ATX) lysophospholipase D has been identified as an 'autocrine motility factor' for tumour cells. The tumour microenvironment (TME) serves a critical role in cancer development, with ATX, as a component of the ATX/lysophosphatidic acid (LPA) axis, integrated into a complex network of molecular signalling. This axis is particularly significant because it activates multiple overlapping signal transduction pathways, thereby mediating pleiotropic effects across nearly all cell types within the TME. The ATX/LPA pathway has multiple molecular and cellular drivers, making the signalling mechanisms activated by ATX/LPA an interesting subject for evaluation in cancer development. The present review discusses the multiple effects of ATX/LPA on three macroevents involving several TME components: i) Inflammation and immunity; ii) cellular proliferation and metabolism; and iii) invasion and metastasis. The aim of the present review was to highlight the clinical impact of the ATX/LPA pathways in the pathogenesis of cancer. Clarifying the role of ATX and blocking this pathway in the inflammatory cycle may open novel therapeutic avenues to improve cancer treatment. Although several reviews have addressed the ATX/LPA axis in cancer, most have focused primarily on its roles in tumour growth, migration and metastasis. By contrast, the present review provides an updated, integrative perspective that emphasizes recent advances (2020-2025) regarding the role of the ATX/LPA axis in shaping the immunometabolic landscape of the TME, with particular attention to inflammation-driven immune regulation.

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Contents

1. Introduction

Cells within the TME are highly plastic and continually change their phenotypic and functional characteristics. Cancer development is a multistep process during which genetic alterations confer specific growth advantages. The role of the TME is crucial in cancer development and is associated with the emergence of inflammation. This distinctive feature of cancer was hypothesised as early as the 19th century by Rudolf Virchow, who regarded the presence of leukocytes as the first indication of a potential association between inflammation and malignancy. However, it was not until the 1990s, following extensive research, that compelling evidence emerged demonstrating that inflammation plays a critical role in tumorigenesis (1). The relationship between inflammation, innate immunity, and cancer is now widely recognised; indeed, inflammation predisposes tissues to cancer development and promotes all stages of tumorigenesis (2). Within the TME, cancer cells interact in a highly coordinated manner with stromal and inflammatory cells to establish a dynamic cellular network (3). More recent evidence supports the concept of the TME as a dynamic immunoregulatory ecosystem, in which inflammatory signalling, stromal remodelling, and immune-metabolic reprogramming collectively shape tumour evolution and therapeutic response (4). Nevertheless, several molecular and cellular mechanisms underlying these interactions remain unresolved, including the role of the autotaxin-lysophosphatidic acid (ATX/LPA) axis, which is the focus of this review. Emerging studies have identified the ATX/LPA axis as a critical regulator of tumour immune escape. Increased ATX expression and LPA production have been associated with reduced $CD8^+$ T-cell infiltration and resistance to immune checkpoint blockade, whereas pharmacological inhibition of ATX or downstream LPA receptors restores antitumour immune responses in preclinical models (5). One of the key mediators

of reciprocal interactions among cells within the inflammatory microenvironment is LPA, a bioactive phospholipid produced primarily through the cleavage of lysophospholipids by the lysophospholipase D enzyme ATX. The enzymatic generation of LPA in plasma through ATX activity was first described in 1986 (6). ATX is expressed in multiple tissues and is encoded by the human *ENPP2* gene (7). ATX is a 125 kDa glycoprotein that was first isolated in 1992 from A2058 melanoma cells and described as an 'autocrine motility factor' (8). Structurally, ATX is a multidomain protein that is initially synthesised as a pre-proenzyme before being processed into a fully active enzyme. The mature protein consists of a central catalytic phosphodiesterase domain, flanked by two N-terminal somatomedin B-like domains (SMB1-2) on one side and a catalytically inactive nuclease-like domain on the other (9). In particular, the lysophospholipase D activity of ATX appears to depend on a deep hydrophobic pocket within the catalytic domain, which binds the substrate LPC. This structural feature is absent from other phospholipases and enables ATX to associate with the cell surface and deliver LPA directly to cells (10).

Our current understanding of the physiological role of LPA indicates that the ATX/LPA axis exerts pleiotropic effects on inflammation, immunity, cell proliferation, metabolism, and cell migration, among other biological processes. Recent evidence also suggests that the ATX/LPA axis contributes to adaptive resistance to anticancer therapies through tumour-stroma interactions. In particular, cancer-associated fibroblasts (CAFs) can secrete ATX in response to therapeutic pressure, thereby promoting LPA-mediated NF-κB signalling and survival pathways, thereby reducing sensitivity to targeted therapies and chemotherapy (11). As a bioactive lipid molecule, LPA interacts with six distinct G protein-coupled receptors, lysophosphatidic acid receptor (LPAR)1-6, on the cell membrane. These receptors signal through Gq, Gi, and G12/13 proteins and activate downstream pathways involving Rho, PLC, Ras, and PI3K, among others, thereby mediating many of the cellular actions of LPA (12-14).

The first LPA receptor to be identified, in 1996, was LPAR1, which exhibits high affinity for LPA (15). LPAR1 and LPAR2 interact with the G proteins Gαi/o, Gαq, and Gα12/13. Subsequently, an orphan GPCR, later identified as LPAR3, was shown to couple with Gαi/o, Gα12/13, and Gαq. Phylogenetically, LPAR1-3 belong to the same receptor family and preferentially recognise acyl-LPA species rather than alkyl or alkenyl LPA analogues. Other orphan receptors, including the G protein-coupled purinergic receptor 9 (p2y9/GPR23), GPR92, which mediates LPA signalling through Gα12/13 and Gαq, and p2y5, which transduces signalling through Gαi and Gα12/13, have subsequently been identified as LPAR4, LPAR5, and LPAR6, respectively (16). These molecular signalling pathways are of considerable importance because they activate multiple overlapping signal transduction cascades and exert pleiotropic effects in almost all cell types, including neurons (17).

The varied biological responses elicited by LPA in tumour cells are associated with transcriptional upregulation of ATX, resulting in increased LPA levels, enhanced expression of multiple LPA receptor (GPCR) subtypes, and reduced metabolic degradation of LPA (14). In oncology research, several molecular components of the ATX/LPA axis have been identified. Therefore, to identify events involving ATX that contribute to cancer pathogenesis, the present review used PubMed-indexed publications. Using different keywords, beginning with 'ATX', we observed that citations began in 1975, with 1,992 published scientific works identified, of which 1,086 were published within the last 10 years. The analysis also considered additional keywords in association with ATX and identified the corresponding number of published scientific works: Cancer (497), tumour microenvironment (TME) (2,682), inflammation (204), immunity (165), proliferation (183), metabolism (1,169), invasion (135), and metastasis (112). For each association, >50% of the total citations were published within the last decade. Although initial interest focused primarily on the relationship between ATX and metabolism, the largest number of publications was associated with the combination of ATX and TME (2,682). This latter combination identified 1,995 publications from 2016 onwards, representing a 74% increase compared with the initial dataset published from 1974. This trend reflects the growing interest in ATX and the TME, particularly in processes such as inflammation and immune responses, which underlie the proliferation and activation of transformed cells and contribute to the selection of invasive and metastatic clones (Fig. 1) (14).

2. ATX/LPA axis in inflammation and immunity

ATX, as a component of the ATX/LPA axis, is a key contributor within the tumour microenvironment, promoting cancer progression by sustaining the inflammatory process (2). Recent studies further indicate that ATX not only maintains inflammatory signalling but also actively shapes the immunosuppressive tumour microenvironment by regulating immune cell trafficking, metabolic fitness, and cytokine networks (18). Inflammation is a protective host response aimed at eliminating endogenous and/or exogenous insults. The stimuli driving inflammation may be acute or chronic, particularly when the response is inappropriately triggered or poorly controlled. Ideally, following complete resolution, the site of acute inflammation returns to normal both structurally and functionally. However, in tissues with limited regenerative capacity, the injured area is replaced by fibrous tissue (19). Multiple signalling pathways and inflammatory mediators contribute to the activation of inflammatory processes, including NF-κB, Janus kinases/signal transducers and activators of transcription (JAK-STAT), toll-like receptor (TLR), cGAS/STING and mitogen-activated protein kinase (MAPK) pathways, cytokines such as interleukins, interferon, and tumour necrosis factor (TNF)-α, chemokines including C-C motif chemokine ligands and C-X-C motif chemokine ligand, growth factors such as vascular endothelial growth factor (VEGF) and transforming growth factor (TGF)-β, and the inflammasome (20). Beyond classical inflammatory signalling cascades, recent evidence highlights the integration of metabolic rewiring and epigenetic regulation in shaping inflammatory responses within the tumour microenvironment, particularly in myeloid-derived suppressor cells (MDSCs) and tumour-associated macrophages (TAMs) (21).

When acute inflammation fails to eliminate the causative agents, it may progress to chronic inflammation, ultimately leading to tissue destruction, loss of function, chronic disease,

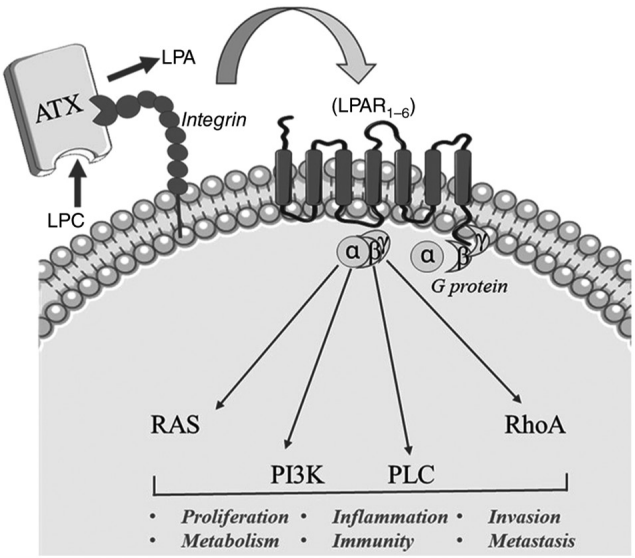

Figure 1. Summary of the role of ATX/LPA in cancer development. ATX hydrolyses LPC to LPA, which binds to its corresponding receptors ($LPAR_{1-6}$), thereby activating various cellular signalling pathways. ATX, autotaxin; LPA, lysophosphatidic acid; LPAR, lysophosphatidic acid receptor; LPC, lysophosphatidylcholine; PLC, phospholipase C; RhoA, Ras homolog family member A.

potential dysplasia, and, in certain cases, cancer (22). Recent integrative reviews further support the causal role of chronic inflammation in tumour initiation and progression, highlighting how persistent inflammatory signalling promotes oncogenic transformation, immune suppression, and tumour evolution (23). The TME is as an ecosystem comprising tumour cells that interact with diverse stromal elements, including the extracellular matrix (ECM), blood-lymph networks, fibroblasts, adipocytes, and immune cells. Central to this interaction between tumour cells and their microenvironment is the ATX/LPA axis (24). ATX/LPA signalling promotes the production of additional cytokines and the recruitment of cells into the local tissue environment, thereby exacerbating the underlying disease. Inflammatory cells form part of a population known as tumour-infiltrating myeloid cells (TIMs), which are associated with CAFs, integral stromal components of the TME. TIMs primarily include macrophages, dendritic cells (DCs), and lymphocytes, which, together with fibroblasts, produce key molecular factors, including pro-inflammatory cytokines, TNF, interleukins, and chemokines (1).

Although the ATX/LPA axis has an established role in regulating inflammation, its function in tumour immunity has received limited attention until emerging studies suggested that this signalling pathway may enable tumour cells to evade immune detection and eradication. Mechanistically, ATX-derived LPA has been shown to limit cytotoxic T-cell infiltration into tumours and promote resistance to immune checkpoint blockade, further supporting its role as a central regulator of tumour immune escape (5). The ATX/LPA axis may therefore be conceptualised as a central node linking chronic inflammation, immunometabolic reprogramming, and immune escape, ultimately driving tumour progression and adaptive therapeutic resistance within the TME. Indeed, ATX/LPA signalling through different LPARs (1-6) may suppress the cytolytic activity of natural killer (NK) cells against tumour cells, impair antigen-driven activation and proliferation, reduce tumour cell killing, and limit the migration of $CD8^+$ T cells into the TME. Furthermore, the effective recruitment of TAMs into the TME may provide an additional source of LPA (17). The phenotypic heterogeneity and functional plasticity of TIMs and CAFs in the TME have complicated efforts to understand how these cellular components use the ATX/LPA axis to communicate, amplify, and dysregulate inflammatory signalling in neoplasms.

Macrophages. Macrophages present in the TME can be classified into three primary categories: Monocyte-derived TAMs, MDSCs and tissue-resident macrophages. TAMs are a highly plastic and heterogeneous population within the TME and may account for up to 50% of cells in certain solid tumours. In the majority of cases, TAMs facilitate disease progression by providing malignant cells with trophic and nutritional support. They exhibit a high degree of functional plasticity and rapidly adapt to microenvironmental perturbations, such as those occurring during tumour progression and in response to (immuno) therapeutic intervention (25). ATX/LPA is induced in immune cells, including human peripheral blood mononuclear cells, monocytes and monocyte-derived DCs, in response to lipopolysaccharide (LPS)-mediated activation of TLR, a key component of infectious and inflammatory responses, through an autocrine-paracrine type I interferon loop involving the JAK-STAT and PI3K-Akt pathways (26). A growing body of evidence suggests that dysfunction of ATX/LPA axis signalling plays a significant role in macrophage function within the TME by regulating monocyte differentiation, macrophage recruitment and the acquisition of pro-tumoral functions. In this context, LPA has been shown to promote monocyte differentiation into macrophages via the Akt/mTOR pathways (27).

Beyond activation of canonical Akt/mTOR signalling, emerging evidence indicates that LPA may contribute to the metabolic reprogramming of TAMs. In particular, lipid metabolic rewiring, characterised by increased fatty acid oxidation, mitochondrial respiration and intracellular lipid accumulation, has emerged as a key determinant of M2-like polarisation and immunosuppressive function in TAMs (28). In this context, LPA-LPAR signalling is likely to support these metabolic adaptations through PI3K/Akt-dependent activation of mTORC1, which coordinates lipid biosynthesis and uptake (29). These lipid-enriched macrophages display pro-tumoral features, including increased expression of arginase-1, IL-10 and pro-angiogenic factors. Furthermore, LPA signalling may intersect with peroxisome proliferator-activated receptor (PPAR)γ-dependent transcriptional programmes, further reinforcing alternative macrophage polarisation and sustaining an immunosuppressive TME.

TAMs may promote tumour cell migration through EGF, stimulate proliferation via platelet-derived growth factor and enhance angiogenesis mediated by VEGF. Within the TME, LPA stimulates the production of IL-6 and IL-8 by tumour cells, thereby amplifying the recruitment of additional macrophages (18). Emerging evidence also indicates that alterations in lipid metabolic pathways within the TME contribute to TAM activation and immunosuppressive phenotypes, highlighting a metabolic dimension of ATX/LPA-mediated

macrophage regulation (30). Moreover, through reciprocal interactions between tumour cells, stromal components and immune cells, LPA signalling contributes to the establishment of a feed-forward loop in which TAMs and cancer cells reinforce a pro-tumoral microenvironment, ultimately promoting tumour progression and metastatic dissemination (31).

DCs. DCs are highly efficient antigen-presenting cells that link innate and adaptive immunity. They express various LPA receptors that mediate chemotaxis, cytokine production and cell-surface receptor expression. In DCs, ATX/LPA signalling differentially modulates the production of cytokines such as IL-12, IL-6, IL-8, TNFα and IL-10, thereby influencing subsequent T cell polarisation (32,33). LPA produced and present in plasma inhibits the surface expression of CD1, a lipid antigen-presenting molecule in DCs, in a PPAR-dependent manner, reducing the ability of DCs to activate T cells (34). Thus, the ATX/LPA pathway can either stimulate or inhibit DC function, depending on the immunological context and the receptors expressed.

Within the TME, tumour-associated DCs (TADCs) differ clearly from TAMs; indeed, they display an immature phenotype and are unable to properly stimulate T cells. This altered behaviour of TADCs is reflected by the lack of effective maturation signals, resulting in poor responses to tumour antigens (35). Therefore, in tumours, DCs do not effectively fulfil their fundamental role in enhancing the immune response (36).

Lymphocytes. The predominant lymphocyte population in the TME comprises T cells, which often exhibit a 'memory' phenotype. Early studies reported a cytokine profile enriched in interleukins such as IL-4 and IL-5, rather than IFN-γ, suggesting skewing towards type 2 helper T cell-associated responses, which are generally considered less effective in antitumour immunity (37). ATX is induced in response to TLR activation by LPS through an autocrine-paracrine type I IFN loop involving the JAK-STAT and PI3K-Akt pathways (26). ATX is highly expressed in lymph node stromal cells and promotes interstitial T cell migration into lymph nodes, primarily through LPA2 signalling (38). One model suggests that LPA generated locally via the ATX/LPA axis provides a chemokinetic 'boost' that facilitates T cell egress from the circulation and entry into lymph nodes along chemotactic gradients established by canonical lymph node-associated cytokines (39).

In the context of cancer, dysregulated ATX/LPA signalling may similarly influence T cell trafficking and positioning within the TME, potentially contributing to impaired tumour infiltration or altered effector functions. Collectively, these data support the concept that the ATX/LPA axis represents an additional layer of regulation of T cell dynamics, with important implications for antitumour immunity and responsiveness to immunotherapeutic strategies. Recent evidence indicates that ATX/LPA signalling can inhibit chemotaxis of cytotoxic $CD8^+$ T cells within the TME: LPA generated by tumour cells limits the migration and intratumoral infiltration of $CD8^+$ TILs, predominantly through LPAR6-mediated pathways, thereby impeding antitumour immunity (40). Furthermore, upregulation of ATX and aberrant LPA signalling have been implicated in resistance to immune checkpoint blockade, with LPA engagement of LPAR5 on $CD8^+$ T cells diminishing their effector functions and correlating with reduced TIL infiltration. Pharmacological inhibition of ATX or LPAR5 can restore effective $CD8^+$ T cell responses and enhance sensitivity to anti-PD-1 therapy (5).

In addition to its role in immune suppression, increasing preclinical evidence supports the therapeutic potential of targeting the ATX/LPA axis in combination with immune checkpoint blockade. Mechanistically, this synergistic effect is hypothesized to rely on ATX inhibition reducing extracellular LPA levels, thereby relieving LPAR5-mediated suppression of cytotoxic T cells and restoring both their metabolic fitness and tissue infiltration. In this context, ATX blockade acts upstream of immune checkpoint signalling by reprogramming the TME into a more permissive immune niche, ultimately enhancing responsiveness to PD-1/PD-L1 inhibitors (5,41). In parallel, recent studies have demonstrated that LPA directly modulates $CD8^+$ T cell metabolism, leading to impaired immunosurveillance and reduced antitumour activity (41). This metabolic dysfunction further contributes to T cell exhaustion and ineffective immune responses within the TME, highlighting a dual role of the ATX/LPA axis in both functional suppression and metabolic reprogramming of cytotoxic T cells.

Importantly, inhibition of ATX or downstream LPA receptors has been shown to restore T cell trafficking and effector function within the TME, effectively converting 'immune-excluded' tumours into 'inflamed' phenotypes. Notably, preclinical models of melanoma and lung cancer have demonstrated that pharmacological inhibition of ATX enhances the efficacy of anti-PD-1 therapy, resulting in improved tumour control compared with monotherapy (5). These findings suggest that the ATX/LPA axis acts as a non-redundant immunosuppressive pathway.

Fibroblasts. Among the components of the TME, fibroblasts constitute the most heterogeneous and abundant population of mesenchymal cells. Fibroblasts are known to be present from the onset of tumour formation through to the final stages of metastatic spread; however, their precise functional role remains incompletely understood (42). During the early phases of oncogenesis, fibroblasts undergo activation and differentiate into CAFs, which accumulate around tumour cells and contribute to the formation of a distinct ECM through a process referred to as the desmoplastic reaction (43). Key characteristics that distinguish CAFs from quiescent fibroblasts include metabolic reprogramming, which supports increased proliferation and enhanced biosynthetic activity (42).

The most well-characterised source of CAF activation is the conversion of resident 'normal' fibroblasts, which, owing to their inherent heterogeneity, comprise distinct subsets. These subsets likely reflect differences in cellular phenotype and tissue of origin, and consequently in the signalling mediators and activation mechanisms involved (44,45). Thus, the heterogeneous nature of CAFs is shaped by the microenvironment, in which multiple signalling pathways are activated, including TGF-β-dependent mechanisms and bidirectional crosstalk between fibroblasts and tumour cells. Furthermore, CAFs may exhibit an anti-inflammatory phenotype during the early stages of tumour transformation and subsequently acquire a

pro-inflammatory phenotype associated with expression of the *ENPP2* (ATX) gene, a key component of the ATX/LPA axis involved in tumour development and progression (46-48).

ATX/LPA-mediated generation of CAFs requires the activation of multiple signalling pathways, including Rho-kinase (ROCK), ERK, PLC, and PI3K. During tumour progression, CAFs emerge as key regulators of dysregulated collagen turnover, leading to desmoplasia and tumour fibrosis, which are associated with poorer patient outcomes. Indeed, when stimulated by LPA, lung fibroblasts release high amounts of type I and type VI collagen, as well as fibronectin, with effects comparable to those observed in response to TGF-β1 (31,49).

The relationship between ATX and TGF-β is particularly evident in pancreatic ductal adenocarcinoma (PDAC). Blocking TGF-β signalling induces the differentiation of CAFs towards an inflammatory phenotype (iCAFs). These iCAFs are responsible for substantial ATX secretion, leading to increased LPA–NFκB signalling in tumour cells. Thus, TGF-β and ATX act in concert in PDAC: TGF-β stimulates fibroblast activation, whereas ATX promotes LPA production, which in turn further supports the fibrotic and aggressive phenotype of CAFs (11). Furthermore, ATX/LPA induces the expression of pro-inflammatory cytokines, such as IL-6, linking the ATX/LPA and IL-6 pathways in an amplification cycle in human dermal fibroblasts (50). The protumorigenic action of ATX/LPA in CAFs is manifested not only through its LPA-producing activity but also through its LPA chaperone function, suggesting a potential mechanism underlying the antitumour effects of ATX inhibition (51). The main mechanisms of LPARs expression across cell types of TME are summarized in Table I.

3. ATX/LPA axis in cell proliferation and metabolism

Tumour initiation and progression require metabolic reprogramming of tumour cells, enabling them to autonomously adjust metabolic fluxes across pathways to meet increased bioenergetic and biosynthetic demands while mitigating oxidative stress that is necessary for proliferation and survival. Cancer-driving mutations, together with the availability of environmental nutrients, further regulate flux through these metabolic pathways. In this context, the TME, often characterised by nutrient depletion, compels tumour cells to adapt by activating mechanisms of nutrient acquisition to sustain proliferation (52).

The TME consists of a complex network of cellular components, including tumour cells, immune cells, endothelial cells, fibroblasts, and adipocytes, as well as molecular components such as cytokines and metabolites, and develops under conditions of stress such as hypoxia and nutrient deficiency. Lipid metabolic reprogramming in both tumour and immune cells within the TME has been extensively investigated, with ATX/LPA signalling emerging as a key mediator linking extracellular lipid metabolism to intracellular metabolic adaptation (53,54). Notably, the ATX/LPA axis is considered an extrinsic stimulus that drives metabolic reprogramming of cancer cells towards a glycolytic phenotype.

Hypoxia-induced oxidative stress, mediated through activation of hypoxia-inducible factor 1α (HIF1α), plays a central role in reprogramming cancer cell metabolism towards enhanced glycolysis. This metabolic shift to aerobic glycolysis, known as the Warburg effect, leads to extracellular H^+ accumulation and intratumoral acidosis (31). The pro-glycolytic effects of ATX/LPA involve a mechanism comprising: i) binding of LPA to an LPA receptor coupled to a Gαi2 subunit; ii) activation of the Rac-NADPH oxidase (NOX)-reactive oxygen species (ROS(pathway, resulting in increased HIF1α levels; and iii) HIF1α-driven upregulation of glucose transporter-1 (GLUT1) and the glycolytic enzyme hexokinase-2 (HKII) (55).

Particularly relevant is the hypoxic state of adipose tissue in breast cancer, where hypoxia functions as a key mediator of communication between adipocytes and adjacent tumour cells. Under hypoxic conditions, metabolic reprogramming of adipocytes enables breast cancer cells to maintain a hypoxic microenvironment. This state is reinforced by adipocyte hypertrophy, which obstructs capillaries, reduces blood flow, and promotes inflammation, endothelial dysfunction, and decreased oxygen availability. Saturated fatty acids may stimulate adenine nucleotide translocase, thereby increasing uncoupled mitochondrial respiration and, consequently, elevating adipocyte oxygen consumption (56).

In this setting, adipocyte-derived ATX may contribute to adipose tissue expansion and increased plasma LPA levels, thereby influencing breast cancer progression, particularly given the predominantly adipose nature of the tumour stroma (57). Inflammatory mediators produced by breast cancer cells have also been shown to enhance ATX production in adipose tissue, which in turn amplifies the production of inflammatory mediators in both adipose and tumour compartments, establishing a self-reinforcing inflammatory cycle (58). This feed-forward loop links inflammation, ATX expression, and LPA production, further driving pro-inflammatory signalling. Beyond supporting tumour growth, this ATX/LPA-driven metabolic-inflammatory circuit also promotes immunometabolic remodelling of the TME, facilitating immune evasion and creating conditions favourable for metastatic dissemination. Signalling pathways involving TNF-α, NF-κB, and ATX expression are positively correlated in breast cancer patients and contribute to increased clonogenicity (59).

In addition to breast cancer, ATX/LPA signalling is frequently upregulated in ovarian and pancreatic cancers. In high-grade serous ovarian cancer, the ATX/LPA axis promotes glycolytic metabolism through a pseudohypoxic response involving Rac-mediated activation of NOX and generation of ROS, which in turn activate HIF1α. Activated HIF1α induces expression of GLUT1 and HKII, reinforcing the glycolytic phenotype (55).

In pancreatic cancer, particularly PDAC, a lipid metabolic shift occurs within the tumour stroma. Pancreatic stellate cells, upon differentiation into CAFs, secrete high levels of lysophosphatidylcholines. These lipids are hydrolysed by tumour-derived ATX to generate mitogenic LPA signals, which activate downstream pathways associated with proliferation and survival (60).

Overall, the metabolic reprogramming of tumour cells highlights the ATX/LPA axis as a promising therapeutic target to enhance treatment efficacy in these aggressive cancers. In Table II, we summarize metabolic reprogramming in the TME by the ATX/LPA axis. This table highlights various aspects related to breast, ovarian, and pancreatic cancer.

Table I. Summary of LPAR subtype expression, downstream phenotypic effects and key signalling/secreted mediators across major tumour microenvironment cell populations.

Cell type	Dominant LPAR expressed	Primary downstream phenotypic effects	Key signalling/ secreted mediators	(Refs.)
TAMs	LPAR6, LPAR1/3	Pro-tumorigenic M2 polarization, suppressed T-cell cytotoxicity and enhanced macrophage recruitment feed-forward loops.	Secretion of IL-6, IL-10 and autotaxin via AKT/mTOR and PPARγ activation.	(1,2,18, 27,28,30)
CAFs	LPAR1, LPAR3, LPAR4	Enhanced fibroblast activation, increased extracellular matrix deposition/stiffness and increased tumour cell invasion/metastasis.	Secretion of amphiregulin and IL-6 via Gi/Rho and YAP/Zeb1 axes.	(3,4,11, 42-44)
T cells ($CD8^+$/naïve)	LPAR5, LPAR1	Impaired TCR calcium signalling, blocked naïve T cell activation and structural exclusion from the tumour nest.	Inhibition of T cell receptor activation and blockade of cytotoxic granule exocytosis	(5,38-41)
DCs	LPAR1, LPAR3	Impaired antigen presentation, reduced DC maturation and induction of tolerogenic DCs that recruit regulatory T cells.	Suppressed costimulatory molecule expression and altered local cytokine milieu.	(24,32-35)

CAF, cancer-associated fibroblast; DC, dendritic cell; Gi/Rho, inhibitory G protein and Rho family of small GTPases; LPAR, lysophosphatidic acid receptor; PPARγ, peroxisome proliferator-activated receptor γ; TAM, tumour-associated macrophage; TCR, T-cell receptor; YAP/Zeb1, Yes-associated protein and zinc finger E-box binding homeobox 1.

4. Role of the ATX/LPA axis in invasion and metastasis

Since its initial identification in the early 1990s, ATX has been recognised as a protein that promotes tumour cell growth and motility. ATX/LPA signalling has been reported to influence not only tumour formation and progression, but also metastasis (61). As metastasis represents a major cause of mortality in patients with cancer, elucidating its underlying mechanisms would constitute a significant advance. Consequently, numerous studies have focused on understanding metastatic spread, a critical event in cancer progression. Within the prometastatic cycle, the interplay among inflammation, cytokines, and chemokines in the tumour microenvironment has been shown not only to promote tumour growth but also to facilitate metastasis. Inflammation increases ATX levels, thereby enhancing LPA production, which in turn further amplifies inflammatory responses (59).

In breast cancer, the increased motility and invasive capacity induced by ATX are mediated by several signalling pathways, highlighting its multifunctional role. These include the gp130/JAK/STAT3 pathway, the PI3K/PAK1/MAPK pathway, the β-arrestin/Ral pathway, the ROCK/non-muscle myosin II pathway, and the ATX/integrin binding pathway (58). Consistently, lung and breast tumours express ATX and display elevated levels of P-selectin, integrin αvβ3, VEGF, and basic fibroblast growth factor. Moreover, breast cancer cells express high levels of LPA, ATX, and PD-L1 (62).

A critical step in metastatic dissemination involves interactions between circulating tumour cells (CTCs) and platelets. Platelets are key mediators of thrombosis and haemostasis that interact with tumour cells, protecting them from mechanical damage caused by haemodynamic shear stress and from NK cell-mediated lysis, while promoting colonisation and metastasis to distant organs. Metastatic tumour cells can induce tumour cell-induced platelet aggregation (TCIPA) through mechanisms involving P-selectin, β3 integrins, and the production of various factors, including LPA (63). Understanding the mechanisms and interactions among these factors is essential for investigating colonisation of distant organs and for developing targeted therapies.

Notably, in several cases, LPA is not produced by CTCs, which may not express ATX, indicating that LPA generated during TCIPA originates directly from aggregated platelets. The platelet ATX/LPA axis may therefore function as a paracrine signal that promotes tumour cell migration and the secretion of pro-inflammatory and pro-osteoclastic cytokines and growth factors (64). A cooperative effect between exogenous ATX and β3 integrin in promoting cell migration has been demonstrated. The binding of ATX to integrins facilitates its internalisation and redistribution to the leading edge of migrating cells. This suggests that integrin β3 binding localises ATX activity to the tumour cell or platelet surface, allowing LPA generation proximal to its receptors and thereby promoting tumour cell dissemination (65).

During the prometastatic cycle, TCIPA formation in the circulation facilitates both immune evasion and microvascular arrest of tumour cells at distant sites. Recent observations indicate that, within metastatic niches, particularly in bone metastases, tumour cells locally convert LPA precursors into LPA with the assistance of ATX (18). Bone metastases are frequently observed

Table II. Comparative schematic table focusing on the reprogramming of OXPHOS and amino acid metabolism mediated by the ATX/LPA axis in breast cancer, ovarian cancer and PDAC.

Tumour type	Stromal and inflammatory drivers	OXPHOS reprogramming	Amino acid metabolism	Phenotypic impact and immune evasion	(Refs.)
Breast cancer	Metabolic ecosystem and cytokines; macrophage-driven inflammation; fibroblast heterogeneity (CAFs)	LPA-stimulated stromal lipolysis; free fatty acids for oxidation; enhancement of mitochondrial OXPHOS	Accelerated glutamine uptake; TCA cycle anaplerosis; upregulation of the serine pathway	Epithelial-mesenchymal transition; antistress glutathione synthesis; resistance to hormonal therapies/chemotherapy; local T-cell suppression	(1,4,12,14,24,28, 31,41,43,45)
Ovarian cancer	High levels of IL-6 and IL-8 in ascites; TME interaction; myeloid cell recruitment	Metabolic flexibility (Warburg/OXPHOS); OXPHOS persistence in hypoxia; maintenance of tumour stemness	Tryptophan degradation (kynurenine); stromal amino acid deprivation; coupled glutamine consumption	Blockade of $CD8^+$ T-cell chemotaxis; reduced lymphocyte infiltration; resistance to platinum-based drugs; dissemination and motility	(3,4,8,12,14,21, 31,33,35,37, 40,41)
Pancreatic cancer (PDAC)	Adaptive stromal secretion of ATX; stromal resistance to TGFβ inhibitors; desmoplasia and severe hypoxia	Preservation of mitochondrial complexes; active OXPHOS in resistant niches; adaptive bioenergetic integrity	Macropinocytosis and autophagy induced by LPA; extracellular amino acid scavenging; non-canonical glutamine metabolism	Tolerance for nutrient deficiency; anti-PD-1 immune resistance via LPAR5; macrophage polarization; inhibition of cytotoxic T cells	(3-5,11,12,14, 27,30,31,40,44)

ATX, autotaxin; CAF, cancer-associated fibroblast; LPA, lysophosphatidic acid; LPAR, lysophosphatidic acid receptor; OXPHOS, oxidative phosphorylation; PD-1, programmed cell death protein 1; PDAC, pancreatic ductal adenocarcinoma; TCA, tricarboxylic acid; TME, tumour microenvironment.

in advanced stages of several solid tumours, particularly breast and prostate cancers, which exhibit strong osteotropism. However, bones are also a common secondary site for disseminated tumour cells (DTCs) originating from lung, thyroid, and kidney cancers. Bone metastasis is initiated by the homing of CTCs to the bone marrow, where they form DTCs (66).

DTCs may either rapidly progress to overt bone lesions or remain dormant for prolonged periods, ranging from 5-30 years, before re-entering an aggressive growth phase. This reactivation appears to require periostin (POSTN), an ECM component expressed by fibroblasts in both normal tissue and the tumour stroma. Tumour cells must induce stromal POSTN expression at secondary sites to enable colonisation, and inhibition of POSTN function has been shown to prevent metastasis (66,67). Accordingly, it is plausible to hypothesise that platelet-coated CTCs activate the ATX/LPA axis, thereby stimulating POSTN expression in stromal cells within the metastatic niche and promoting tissue colonisation (68).

In this context, osteoclasts play a central role as the only cells capable of resorbing bone matrix. Their activity drives bone destruction in multiple malignancies, including multiple myeloma and other tumour types (69). LPA produced by tumour cells following bone colonisation acts in a paracrine manner on tumour receptors, promoting proliferation and the secretion of pro-osteoclastic cytokines (IL-6 and IL-8), thereby contributing to bone resorption either directly or indirectly through activation of osteoclastic receptors such as LPA1. However, the mechanisms by which ATX influences osteoclast function remain incompletely understood (64).

Recent preclinical evidence indicates that ATX expressed by myeloid ($LysM^+$) cells significantly promotes metastatic dissemination, and that its deletion reduces lung metastases in melanoma models. This highlights the contribution of non-tumour sources of ATX to metastasis (70). Furthermore, elevated ATX/LPA signalling has been associated with poorer clinical outcomes in patients with resectable gastric carcinoma, suggesting its potential as a predictive biomarker of disease progression (71). LPA is increasingly recognised as an oncometabolite that enhances tumour cell migration, invasion, and metastatic dissemination, making its metabolic pathways and receptor interactions attractive therapeutic targets (72).

Collectively, these findings support the concept that ATX/LPA-driven metastasis is not solely a tumour cell-intrinsic process, but rather the result of coordinated metabolic, inflammatory, and stromal interactions that shape a permissive metastatic niche. Emerging preclinical studies further demonstrate that pharmacological inhibition of ATX (such as PF-8380) can reduce metastatic phenotypes and enhance the efficacy of other anticancer therapies, underscoring the therapeutic potential of targeting the ATX/LPA axis beyond the primary tumour (73).

5. Future implications of the ATX/LPA axis in clinical practice

To date, cancer treatment has primarily relied on therapies that inhibit tumour cell proliferation and survival. However, accumulating evidence indicates that components of the TME are key contributors to tumour development and to the modulation of therapeutic responses. Based on the data presented in this review, the ATX/LPA pathway plays a central role in maintaining the TME by sustaining inflammatory and immune responses, promoting cell migration, invasion, and metastasis, and contributing to tumorigenesis. Numerous studies also support its involvement in chemotherapy resistance (74). Therefore, inhibition of the ATX/LPA pathway may represent a novel therapeutic strategy by targeting both tumour cells and components of the TME.

Several ATX inhibitors have been evaluated in preclinical and clinical studies, some showing promising results, including PF-8380, GLPG1690, and IOA-289. PF-8380 exhibits potent ATX inhibitory activity by binding to the orthosteric site of ATX, thereby mimicking LPC substrate binding. Originally developed and patented by Pfizer, PF-8380 is now being widely investigated for its capacity to counteract tumour progression and enhance the efficacy of conventional therapies. An *in vitro* study in human and murine glioblastoma cell lines demonstrated that PF-8380 suppresses tumour cell invasion and enhances radiosensitisation via ATX inhibition (75). These findings highlight an anti-ATX/LPA strategy that could be used as an adjunctive treatment to inhibit angiogenesis, increase chemosensitivity, or mitigate adverse effects such as radiotherapy-induced fibrosis.

Another ATX inhibitor previously considered promising is GLPG1690 (ziritaxestat), developed by Galapagos and advanced to Phase III clinical trials in idiopathic pulmonary fibrosis. However, its development was discontinued following the ISABELA Phase III studies (76-78). More recently, IOA-289 has emerged as a novel ATX inhibitor characterised by a unique chemical structure, high potency, and a favourable safety profile. It has been shown to suppress cell growth and migration in *in vitro* models of gastrointestinal tumours (79). In addition, in a mouse model of PDAC, IOA-289 overcame resistance to both the TGF-β receptor inhibitor galunisertib and the nucleoside analogue gemcitabine (11).

6. Conclusions

Cancer is one of the most complex global public health challenges, with an ever-increasing incidence. Therefore, understanding and clarifying the events underlying cellular transformation and cancer evolution remains imperative. Recent evidence has demonstrated that both cellular and non-cellular components of the TME are essential in promoting cancer growth, invasion and metastasis. Accordingly, identifying the numerous pro-tumoral activities of the ATX/LPA axis, which lies at the centre of this complex network, represents an important advance. The present review illustrates how ATX expression in cells within the TME promotes inflammatory signalling. Given that cancer is widely recognised as a chronic inflammatory condition, it is plausible that cancer initiation and progression may also be fuelled by ATX derived from non-malignant cellular sources, including the tumour stroma and surrounding tissues. Collectively, current evidence supports a model in which the ATX/LPA axis integrates chronic inflammation, immunometabolic reprogramming and stromal signalling, thereby coordinating tumour progression, immune escape and metastatic dissemination across multiple stages of cancer evolution. ATX is currently considered a potential therapeutic target in cancer, and a growing number of ATX

inhibitors have been developed. These inhibitors are regarded as promising because they can directly target tumour cells while also modifying the microenvironment, making it less favourable for tumour cell growth and potentially improving the efficacy of other therapies used to overcome drug resistance. In summary, several aspects related to inflammation, proliferation, immunity, metabolism, invasion and metastatic capacity are evaluated. These processes, initiated through ATX/LPA signalling, involve the action of numerous molecular and cellular players, underscoring the pleiotropic role of the ATX/LPA axis. Therefore, the diverse signals transmitted to tumour cells through the ATX/LPA pathway represent important elements for identifying additional pharmacological targets within multidrug therapeutic strategies.

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Competing interests

The authors declare that they have no competing interests.

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