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Autotaxin and chronic inflammatory diseases

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ABSTRACT

Autotaxin (ATX) is a secreted glycoprotein, widely present in biological fluids including blood. ATX catalyzes the hydrolysis of lysophosphatidylcholine (LPC) to lysophosphatidic acid (LPA), a growth factor-like, signaling phospholipid. LPA exerts pleiotropic effects mediated by its G-protein-coupled receptors that are widely expressed and exhibit overlapping specificities. Although ATX also possesses matricellular properties, the majority of ATX reported functions in adulthood are thought to be mediated through the extracellular production of LPA. ATX-mediated LPA synthesis is likely localized at the cell surface through the possible interaction of ATX with integrins or other molecules, while LPA levels are further controlled by a group of membrane-associated lipid-phosphate phosphatases. ATX expression was shown to be necessary for embryonic development, and ATX deficient embryos exhibit defective vascular homeostasis and aberrant neuronal system development. In adult life, ATX is highly expressed in the adipose tissue and has been implicated in diet-induced obesity and glucose homeostasis with multiple implications in metabolic disorders. Additionally, LPA has been shown to affect multiple cell types, including stromal and immune cells in various ways. Therefore, LPA participates in many processes that are intricately involved in the pathogenesis of different chronic inflammatory diseases such as vascular homeostasis, skeletal and stromal remodeling, lymphocyte trafficking and immune regulation. Accordingly, increased ATX and LPA levels have been detected, locally and/or systemically, in patients with chronic inflammatory diseases, most notably idiopathic pulmonary fibrosis (IPF), chronic liver diseases, and rheumatoid arthritis. Genetic and pharmacological studies in mice have confirmed a pathogenetic role for ATX expression and LPA signaling in chronic inflammatory diseases, and provided the proof of principle for therapeutic interventions, as exemplified by the ongoing clinical trials for IPF.

1. Introduction

ATX was first isolated from the supernatant of highly metastatic melanoma cells and was characterized as an autocrine motility-stimulating factor [1]; since, many studies have explored its role in cancer growth and metastasis [2–5]. In the same context, a major role for ATX has been proposed in resistance to chemotherapy, suggesting ATX targeting as an adjuvant therapy [6,7].

ATX genetic deletion and abrogation of LPA production resulted in embryonic lethality, due to the aberrant vascular homeostasis and neural tube defects indicating a major role of ATX/LPA in embryonic, vascular and neuronal, development [8–10]; non-catalytic effects of ATX in development have been also reported including the modulation of oligodendrocyte physiology and the localization and adhesion of neuronal progenitors [11–13]. Remarkably, embryonic transgenic overexpression of ATX also resulted in lethality, arguing for the importance of tightly regulating LPA levels during development [14]. No single LPA receptor knock out mouse was able to reproduce the phenotype of ATX deficient embryos [8,9], suggesting combinatorial LPA signaling during development. Moreover, ATX is highly expressed in the reproductive organs, while increased ATX levels have been detected in human pregnancy, suggesting a role for ATX in reproduction [15,16].

In this review, we focus on the emerging role of ATX expression and LPA signaling in chronic inflammatory diseases and the therapeutic potential of pharmacologically targeting ATX.

2. Autotaxin (ATX, *ENPP2*)

ATX is encoded by the *ENPP2* gene residing in the human chromosomal region 8q24, a region that contains potential susceptibility

Abbreviations: ATX, ENPP2: Autotaxin; lysoPLD, lysophospholipase D; PLA_2, phospholipase A_2; LPC, lysophosphatidylcholine; LPA, lysophosphatidic acid; S1P, sphingosine-1-phosphate; GPCRs, G-protein-coupled receptors; LPARs, LPA receptors; PLPPs, lipid-phosphate phosphatases; HEVs, high endothelial venules; CSF, cerebrospinal fluid; BALF, bronchoalveolar lavage fluid; IPF, idiopathic pulmonary fibrosis; CLDs, chronic liver diseases; RA, rheumatoid arthritis

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loci for different types of cancer; the highly homologous (93%) mouse *Enpp2* gene is in chromosome 15. Several pro-inflammatory factors (LPS, TNF, IL-6, galectin-3), transcription factors (Hoxa13-Hoxd13, v/c-jun, Stat3, AP-1, NFAT1, NF-kB) and epigenetic modifiers (HDACs) have been suggested to regulate *ENPP2/Enpp2* transcription, while the HuR and AUF1 RNA-binding proteins have been suggested to control its mRNA stability [3,17]. LPC, the enzymatic substrate of ATX, has been shown to be a potent ATX inducer in hepatocytes [18], while LPA, the enzymatic product of ATX, has been suggested to negatively regulate ATX expression, in the absence of inflammatory mediators [19].

In adult healthy life, the highest ATX mRNA levels have been detected in the adipose tissue, the central nervous system (CNS) and the reproductive organs. ATX has been reported to be constitutively expressed from endothelial cells in high endothelial venules (HEVs), regulating lymphocyte trafficking, from choroid plexus and leptomeningeal cells, secreting ATX in the cerebrospinal fluid (CSF), and from bronchial epithelial cells, secreting ATX in the bronchoalveolar lavage fluid (BALF) [3,17]. In chronic inflammatory disorders, ATX has been reported to be expressed from arthritic synovial fibroblasts secreting ATX in the synovial fluid, alveolar inflammatory macrophages, contributing ATX/LPA in the BALF, hepatocytes upon hepatitis, activated astrocytes upon neurotrauma, while ATX has been also detected in peritoneal and blister fluids [3,17]. ATX can also be found in the serum, where almost 40% is thought to originate from the adipose tissue [20,21].

ATX consists of two N-terminal somatomedin B-like domains (SMB1 and SMB2) stabilized by four pairs of disulfide bonds, a central phosphodiesterase (PDE) domain that encompasses its active catalytic site, and a C-terminal nuclease-like domain (NUC) strongly bound to the PDE domain via a 50-residue loop [3,22]. Mutational analysis has identified many important residues for ATX's glycosylation, secretion and catalytic activity [3,22], while its crystal structure has been solved providing many mechanistic insights, and allowing rational drug designing [23–25].

ATX is a secreted, lysophospholipase D (lysoPLD) catalyzing the extracellular hydrolysis of LPC to LPA [26] (Fig. 1). It belongs to the ectonucleotide pyrophosphatase-phosphodiesterase (ENPP) protein family, that hydrolyses phosphodiester bonds of various nucleotides [27]; however ATX is the only family member that gets secreted and that possesses lysoPLD properties. Although ATX also possesses matricellular properties [12], and *in vitro* phosphodiesterase activity, the majority of ATX reported functions in adulthood are thought to be mediated through the extracellular production of LPA [3,28,29]. Moreover, ATX has been suggested to bind to integrins at the cell surface [23,30,31], thus avoiding clearance, and possibly directing LPA to its adjacent receptors and thus localizing LPA effects (Fig. 1).

LPC, the enzymatic substrate of ATX and the major precursor of LPA (Fig. 1), is synthesized by phospholipase A_2 (PLA_2) enzymes from fatty acid or membrane phosphatidylcholine (PC), that also leads to the production of arachidonic acid and sequentially to various pro-inflammatory eicosanoids. Increased PLA_2 expression has been reported in different inflammatory pathophysiological conditions, while LPC was recently shown to stimulate ATX expression in hepatocytes [18], supporting a previously suggested interplay of the PLA2/LPC and ATX/LPA axes [32]. LPC is highly abundant in plasma, predominantly associated with albumin and oxidized low-density lipoprotein (oxLDL) [3,22].

3. Lysophosphatidic acid (LPA)

LPA, the enzymatic product of ATX (Fig. 1), consists of a glycerol backbone, a free phosphate group and a single fatty acyl chain of varying length and saturation. Thus, it is a mixture of saturated (16:0, 18:0) and unsaturated (16:1, 18:1, 18:2, 20:4) species, present at most biological fluids. LPA levels in plasma are much lower (~0.7 μM) than the LPC ones (~200 μM) and with different species distribution (LPA: 18:2 > 20:4 > 18:1; LPC: 16:0 > 18:1/18:0 > 20:4). LPA serum levels are much higher than the plasma ones, due to the ATX-mediated hydrolysis of LPC, and other phospholipids, that are released from activated platelets during coagulation [3,28]. LPA is negatively regulated by a group of membrane-associated lipid-phosphate phosphatases (LPPs) that convert LPA to monoacylglycerol (MAG), counteracting ATX's activity (Fig. 1) [29].

LPA signals through its six cognate receptors (LPAR1-6; Fig. 2) that exhibit widespread, but differential, cell and tissue distribution, as well as overlapping specificities. The orphan GPR87 and P2Y10 receptors, the receptor for advanced glycation end products (RAGE) and the intracellular peroxisome proliferator-activated receptor γ (PPARγ), have also been suggested to transduce LPA signals. LPARs couple with G-proteins, crucial molecular switches that activate numerous signal transduction pathways (Fig. 2). In accordance, many *in vitro* studies have indicated that LPA activates, among others, the production of second messengers through phospholipase C (PLC; via $G\alpha_q$), Rho A-

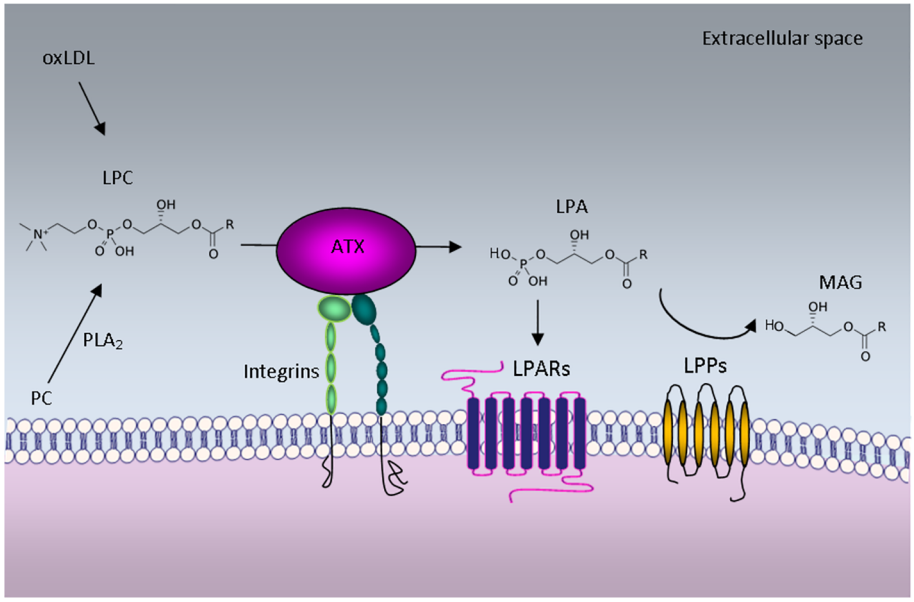

Fig. 1. Schematic representation of the central role of ATX in regulating extracellular LPA metabolism.

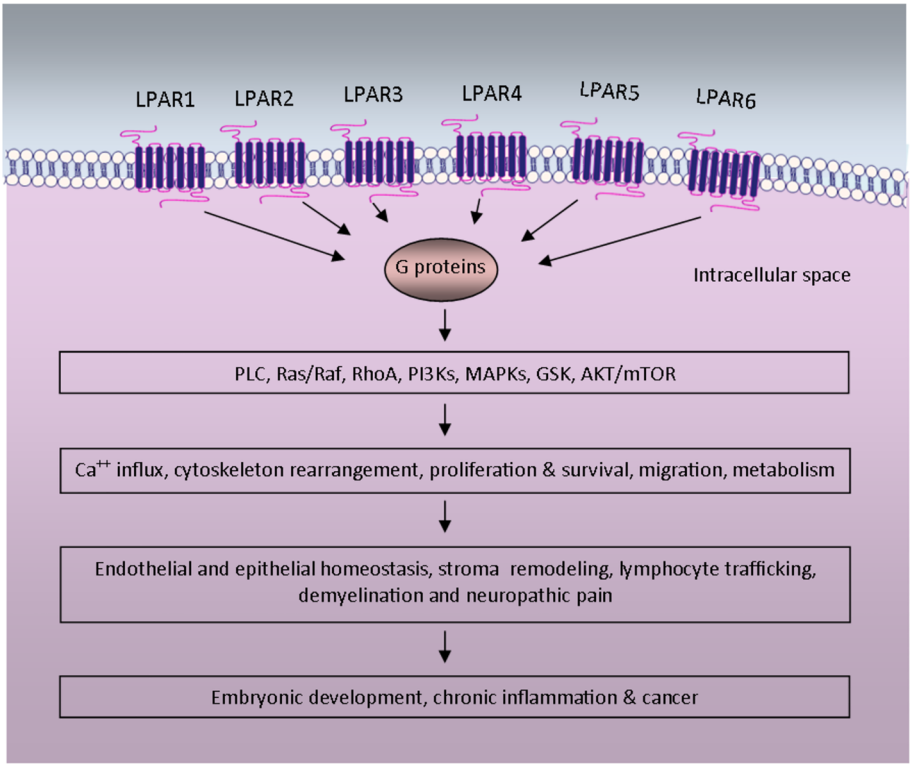

Fig. 2. Schematic overview of the involvement of LPA and GPCR signaling in the pathogenesis of chronic inflammation.

dependent cytoskeletal remodeling (via $G\alpha_{12/13}$), as well as the mitogenic Ras-Raf-MEK-ERK and the pro-survival phosphoinositide 3-kinase pathways (via $G\alpha_i$) (Fig. 2) [3,33,34]. Therefore, any ATX/LPA effect ultimately depends on the spatiotemporal and cell-specific expression profile of the different LPA receptors and the corresponding activation of the specific G protein-mediated cellular pathways (Fig. 2). Moreover, as these pathways have been reported to be co-activated by many different growth factors in different disease settings, synergistic effects can be also envisaged.

4. ATX and LPA signaling in chronic inflammation

The G-protein-mediated mitogenic and pro-survival LPA effects *in vitro* have been long established [35,36]. Central to the LPA effects on proliferation, apoptosis and motility lies its ability to modulate the actin cytoskeleton through the activation of the small GTPases Ras (via G_i) and Rho A (via $G_{12/13}$) (Fig. 2) [37,38]. Beyond these LPA cellular effects, well consistent with the hallmarks of cancer, the ATX/LPA axis has been shown to play important roles in many other pathophysiological processes, highly pertinent to chronic inflammation (Fig. 2), such as vascular homeostasis [39,40], platelet aggregation [41], lymphocyte trafficking [42,43], chronic neuropathic pain [44], skeletal development and remodeling [45,46], and stem cell physiology [47].

Most notably, ATX and LPA have been suggested to play a major role in vascular homeostasis [39,40], exemplified by the vascular developmental effects in mice and zebrafish in the absence of components of the ATX/LPA axis [8–10]. Moreover, a multitude of studies, mostly *in vitro*, have suggested a role for LPA on endothelial physiology, including the promotion of endothelial cell migration, cytokine secretion and leukocyte adhesion [48,49]. In the same context, LPA has been suggested to regulate endothelial barrier functions and permeability; however, opposing results have been reported, both *in vitro* [49,50], as well as *in vivo* [51–53]. Adding an extra layer of complexity, a crosstalk of LPARs and S1P receptors on endothelial physiology has been recently suggested [140].

Importantly, LPA has been reported to regulate lymphocyte trafficking in lymphoid organs [42,43]. ATX is highly expressed in endothelial cells of high endothelial venules (HEVs) [54,55], as well as from fibroblastic reticular cells [56]. ATX itself has been suggested as an adhesive substrate of homing lymphocytes [54], while the locally produced LPA was suggested to modulate endothelial physiology [55]. Moreover, LPA was shown to regulate intranodal T-cell motility [57,58], and to promote lymphocyte transmigration across the basal lamina of HEVs [55]. LPAR2, LPAR4 and LPAR6 on lymphocytes have been suggested to play differential and even opposing roles [56,59].

The fact that ATX is highly expressed in the adipose tissue, with adipose-derived ATX being accountable for 38–50% of plasma LPA [20,21], puts ATX/LPA-induced pathophysiology under a different perspective. Obesity triggers low-grade chronic inflammation that affects multiple organs and may predispose for chronic diseases. Adipocytes are known to secrete peptides (i.e. adipokines) that act as endocrine factors to distant adipose stores and possibly other metabolic tissues to regulate processes such as glucose and lipid homeostasis, insulin sensitivity and inflammation [60]. Although the involvement of ATX/LPA axis in adiposity remains controversial [20,21,61,62], ATX and LPA have been reported to promote glucose intolerance and insulin resistance [62–64]. Moreover, genetic deletion of ATX in the adipose tissue modulated hepatic lipid metabolism and decreased steatosis in an endocrine manner [62]. Therefore, ATX can be suggested as a novel adipokine with multiple implications for chronic inflammatory metabolic disorders.

Given the LPA effects in vascular homeostasis, as well as in obesity and lipid and glucose metabolism, it is not surprising that the ATX/LPA/LPP axis has been linked to cardiovascular diseases and atherosclerosis [50,65,66]. Increased LPA levels have been associated with coronary artery disease, where the LPA-catabolizing protein LPP3 has been proposed as a novel risk factor [65,66]. Haploinsufficient ATX mice, with 50% of normal plasma LPA levels, were prothrombotic, while transgenic mice overexpressing ATX from the liver, with 200% of normal plasma LPA levels, presented with a bleeding diathesis [67],

suggesting a major role for ATX/LPA in hemostasis and thrombosis and further highlighting a feedback loop between LPA and murine platelets [30,67]. Lipoprotein derived ATX has been shown to promote inflammation and mineralization of the aortic valve [68], and circulatory ATX was correlated with high fat diet-induced cardiac dysfunction and hypertrophy [69,70]. LPA was reported to gradually accumulate in atheromatic plaques [71], likely through the ATX-mediated hydrolysis of low density lipoproteins (LDLs)-derived LPC [72]. Furthermore, LPA was suggested to promote atherosclerosis by stimulating CXCL1 expression from the endothelium [72], as well as through the regulation of macrophage physiology [72–74]. Pharmacological inhibition of ATX with PF-8380 attenuated HFD-induced cardiac hypertrophy, dysfunction and inflammatory response [69], suggesting that ATX targeting could be beneficial in cardiovascular diseases.

5. ATX in idiopathic pulmonary fibrosis (IPF)

Multiple effects of LPA on lung pathophysiology have been suggested, likely affecting the pathogenesis of different pulmonary diseases, including asthma and chronic obstructive pulmonary disease (COPD) [3,49,75], as well as lung allograft fibrosis [76].

IPF is a chronic, progressive interstitial lung disease with median survival time of 3–5 years following diagnosis, and a prognosis being worse than many cancers [77]. According to the prevailing theory, pulmonary fibrosis is the result of abnormal, deregulated wound healing in response to environmental pathological stimuli. The injured alveolar epithelium, in order to restore its integrity and functions, secretes multiple mediators that activate the immune system as well as the adjacent pulmonary fibroblasts. Fibroblasts migrate and differentiate into myofibroblasts, that contract the wound and provide ECM components necessary for its re-epithelialization [78]. In pathological conditions and upon persistent epithelial damage, further supported by genetic predisposition and age-dependent epigenetic changes in gene expression, myofibroblasts accumulate, resulting in excessive deposition of collagen and extracellular matrix (ECM), and thus distortion of lung architecture and deterioration of respiratory functions [78]. Recently two new approved drugs, pirfenidone [79] and nintedanib [80] were found to delay the progression of the disease in large multicenter studies.

Increased ATX staining has been reported in fibrotic lungs of human patients and animal models, localized in the bronchial epithelial cells and alveolar macrophages [81], while additional ATX could be extravasated due to the vascular leak accompanying the pathogenesis of fibrosis in mice. Increased ATX levels were also reported in the BALFs of mice treated with bleomycin (BLM) [81,82], the most widely used animal model for pulmonary fibrosis [83,84]. Increased LPA levels were also detected in IPF patients [53]. Conditional genetic deletion of ATX from bronchial epithelial cells or alveolar macrophages, reduced ATX activity in the BALFs and decreased BLM-induced vascular leak, inflammatory cell influx, as well as TGFβ and collagen expression, attributed to the diminished production of LPA [81]. Accordingly, ubiquitous genetic deletion of *Lpar1* [53] or *Lpar2* [85] also attenuated BLM-induced pulmonary fibrosis, attributed to reduced epithelial apoptosis, vascular leak and inhibited fibroblast recruitment. However, conditional genetic deletion of the different LPA receptors at different cell types will be required to fully decipher the likely pleiotropic participation of LPA in IPF pathogenesis.

LPA receptors are widely expressed in pulmonary cells and various LPA effects have been reported in almost all cell types in *in vitro* studies [49,75]; however, their relative contribution to disease pathophysiology *in vivo*, remains to be identified. Most notably, LPA has multiple effects on endothelial physiology and vascular homeostasis [39,40], regulating endothelial permeability and thus the influx of inflammatory cells and soluble mediators. In animal models, disease attenuation in ATX, *Lpar1* and *Lpar2* deficient mice was attributed, among others, to reduced vascular leak [53,81,85]. Noteworthy, vascular abnormalities, such as pulmonary hypertension, affect the overall IPF prognosis, while an interplay of fibrotic mechanisms with the pulmonary vasculature has been suggested [86].

ATX is constitutively expressed in bronchial epithelial cells of both humans and mice [81], while LPA and LPAR1 have been reported to participate in alveolar septal formation during development [87], suggesting a role for ATX/LPA in epithelial functions. Decreased epithelial apoptosis was observed in BLM-treated *Lpar1*$^{-/-}$ and *Lpar2*$^{-/-}$ mice [53,85], and LPA has been suggested to promote epithelial anchorage-dependent apoptosis [88]. Additional LPA effects on epithelial cells that possibly have a role in disease pathogenesis include the induction of IL-8 secretion stimulating neutrophilic influx [89,90], as well as the local activation of TGFβ. TGFβ is the prototype pro-fibrotic factor promoting epithelial cell injury, myofibroblast differentiation and ECM deposition and remodeling [91]. Exposure of normal human bronchial epithelial cells to LPA stimulated stress fibre formation and integrin $\alpha_v\beta_6$ reorganisation leading to TGF-β activation [92,93], suggesting ATX/LPA as a master regulator of TGFβ responses and thus an important profibrotic factor.

Differentiation of lung fibroblasts to myofibroblasts and exuberant ECM production are the main pathologic events in IPF and BLM-induced pulmonary fibrosis [77,78]. Apart from TGFβ activation, LPA has been suggested to participate in the regulation of many pathologic functions of fibroblasts in the context of pulmonary fibrosis, including chemotaxis [53] and resistance to serum-deprivation apoptosis [88]. LPA effects on lung fibroblasts were proposed to be differentially mediated by LPAR1 and 2 [53,85], Pulmonary macrophages were shown to stain for ATX in both human patients and animal models, and genetic deletion of ATX from macrophages (LySM^{+}) reduced the BALF load of ATX, decreasing the severity of BLM-induced pulmonary fibrosis [81]. Both alveolar and interstitial macrophages have been proposed to participate in the pathogenesis of the disease [94,95], while LPA has been shown to stimulate the expression of F4/80, a well-known macrophage activation marker [96], in monocytic CD11b^{+} cells [97], suggesting a role for LPA in the macrophage activation and maturation.

Therefore, ATX-mediated LPA production has been suggested to induce pleiotropic pathogenetic effects in different pulmonary cells, culminating to the pathogenesis of pulmonary fibrosis. In support of the correlational human data and the genetic studies in animal models, many pharmacological studies indicated that ATX inhibition decreased LPA levels and attenuated BLM-induced pulmonary fibrosis (Summarized in Table 3), thus establishing ATX as a therapeutic target in IPF and providing the proof of principle for clinical studies.

6. ATX in chronic liver diseases (CLDs)

CLDs, including alcoholic liver disease (ALD), chronic viral hepatitis (CVH), and non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH), originate from a persistent pathogenetic insult stimulating chronic inflammation. The increased secretion of pro-inflammatory and pro-fibrotic factors promote the differentiation of hepatic stellate cells (HSCs) to myofibroblasts, leading to excessive collagen and ECM deposition. The ensuing fibrosis may lead to cirrhosis, the major risk factor for the development of hepatocellular carcinoma (HCC) [98,99].

Increased levels of serum ATX activity and/or protein levels were found in patients with different CLDs: chronic hepatitis C (CHC), chronic Hepatitis B (CHB), steatohepatitis and NAFLD (summarized in Table 1). ATX levels were reported to correlate with liver fibrosis and stiffness [100], steatosis and insulin resistance [101,102], as well as with disease severity and overall survival [103,104], thus establishing ATX as a diagnostic and/or prognostic marker of different forms of liver fibrosis [105]. Increased ATX levels were also reported in patients with cholestatic disorders, correlating with itch intensity, as well as with disease stage and overall survival in patients with Primary Biliary Cholangitis (PBC) (Table 3). Therefore, ATX/LPA is also strongly

Table 1
ATX/LPA measurements in human patients.

Disease	Samples (n)	Method	Observations	Reference (PMID)
IPF	38 IPF/UIP, 10 fNSIP, 5 cNSIP, 20 COP/OP and 20 control lung tissue core samples in a tissue microarray	Immunohistochemistry	Increased ATX staining in IPF/UIP and fNSIP samples, localised in the hyperplastic epithelium and alveolar macrophages.	22744859
IPF	9 IPF patients and 7 healthy controls BALFs	ESI/MS	Increased LPA levels in patients as compared to controls	18066075
IPF	Exhaled breath condensates (EBCs) from 11 IPF patients and 11 controls	LC-MS/MS	22:4 LPA was significantly elevated in the EBCs of IPF subjects when compared to controls	24468008
RA	Synovial fibroblasts from 15 RA and 2 non-RA patients	Competitive RT-PCR	Increased ATX mRNA in RA compared to OA	11168012
RA	Synovial fluids from 16 RA and 9 OA patients	ELISA	Increased ATX levels in RA patients as compared to OA patients	22493518
RA	Serum samples from 26 RA and OA patients	Activity assay	Increased enzymatic activity ATX levels	22493518
RA	Synovial fibroblasts isolated from 3 RA and 3 OA patients	Q-RT-PCR	Increased ATX levels in RA compared to OA	22493518
RA	8 RA and 8 OA synovial tissue samples	Immunohistochemistry	Increased ATX levels in RA compared to OA	22493518
RA	5 RA and 5 OA synovial tissue samples	Immunohistochemistry	Increased ATX levels in RA compared to OA	25273676
CLDs	Serum from 35 CVH, 12 NASH, and 12 ALD patients, and 20 healthy controls	ELISA	Increased ATX plasma levels in patients vs healthy controls; Association with survival	27981605
CHC	Serum from 41 patients with chronic hepatitis C, and 18 healthy controls	ATX activity assay	Increased ATX activity in patients vs controls	17577119
CHC	Serum from 593 patients with chronic hepatitis C, and 160 controls	ELISA	ATX levels were significantly higher in patients than in healthy controls	28425454
CHC	Serum from 12 chronic HCV patients, and 12 healthy controls,	ELISA	Increased ATX levels in chronic hepatitis C infected with high APRI score vs controls	23507661
CHB	Serum from 101 treatment-naïve patients with HBV-related chronic hepatitis or cirrhosis, and 160 healthy controls	ELISA	Serum ATX concentration increased significantly according to liver fibrosis stage	29114991
NAFLD	Serum from 307 biopsy confirmed patients	ELISA	Serum ATX concentration was significantly correlated with fibrosis stage	31144415
NAFLD	Serum from 37 NAFLD and 64 non-NAFLD obese women	ELISA	Increased ATX levels in patients	25865747
CVH - HCV	Serum from 74 patients with chronic liver disease caused by hepatitis C virus	ELISA	Serum ATX level correlated significantly with liver fibrosis stage	21419756
Cholangitis	Serum from 118 with primary biliary cholangitis (PBC) and 115 with primary sclerosing cholangitis (PSC), and 109 healthy controls	ELISA	Serum ATX levels correlate with bile acid concentrations and itch intensity	27506882
Cirrhosis	Serum from 270 patients with liver cirrhosis and 85 healthy controls	ELISA	Higher ATX levels in patients compared to healthy controls. Elevated ATX levels correlate with disease severity, hepatic decompensation and mortality	25062038
Cholestasis	Serum from 25 cholestatic patients without pruritus, 52 cholestatic patients with pruritus, and 202 healthy controls	ATX activity assay	Higher ATX activity in all cholestatic patients compared to controls. Patients with pruritus had higher ATX activity compared to patients with no pruritus	20546739
Cholestasis	Serum from 40 Cholestatic patients without pruritus, 91 cholestatic patients with pruritus, and 202 healthy controls	ATX activity assay	Higher ATX activity in all cholestatic patients compared to controls. Patients with pruritus had higher ATX activity compared to patients with no pruritus	22473838
PBC	Serum from 128 patients with primary biliary cholangitis, and 160 healthy controls	ELISA	ATX levels of patients with PBC were significantly higher than those of controls	29802350

PMID: PubMed identifier; NSIP: Nonspecific Interstitial Pneumonia; COP/OP: Cryptogenic Organizing Pneumonia; MS: Mass spectroscopy; CLDs: Chronic Liver diseases; ALD: Alcoholic liver disease, CVH: Chronic viral hepatitis, NASH: nonalcoholic steatohepatitis; CHC: chronic hepatitis C; CHB: Chronic hepatitis B; APRI: Aspartate aminotransferase to Platelet Ratio Index. NAFLD: non-alcoholic fatty liver disease; PBC: Primary Biliary Cholangitis.

corelated with cholestasis-associated pruritus [106].

The reported increased levels of ATX in the serum of CLD patients may be partially attributed to decreased clearance of ATX by liver endothelial cells [107], since disease development in the liver abrogates its functions. However, it was recently shown that ATX can be also produced locally and specifically by hepatocytes upon toxin (CCl4 or THC)-induced chronic liver damage [18], suggesting that liver specific production is another cause for the reported increased levels of ATX in the circulation of CLD patients. ATX expression from primary mouse hepatocytes *ex vivo* was shown to be induced by LPC, LPS and TNF, while elevated liver ATX levels were detected upon Concanavalin A induced, T-cell-dependent and TNF-mediated, inflammatory damage *in vivo*, suggesting that inflammation can trigger ATX expression from hepatocytes [18]. Moreover, HCV infection was also reported to stimulate hepatocyte ATX expression, in both mice and humans, correlating with the efficiency of virus replication [18,108,109]. Therefore, different hepatotoxic stimuli associated with different forms of CLDs and the ensuing inflammation can stimulate hepatocyte ATX expression in the liver.

Conditional genetic deletion of ATX specifically in hepatocytes (Alb^+) attenuated disease development in a cytotoxic model of CCl4-induced fibrosis [18], thus indicating a pathogenetic role for hepatocyte ATX expression. It should be noted that transgenic ATX overexpression from hepatocytes (*a1t1)* [110] promoted collagen deposition and fibrosis in the CCl4 model [18], but did not induce any liver pathologic effects without toxic stimulation [18,110], suggesting that ATX expression is not enough to induce liver fibrosis *per se*, but is rather required to amplify pro-fibrotic signals. Remarkably, genetic deletion of ATX in adipocytes decreased steatosis in a High Fat Diet (HFD)-induced NASH model [62] suggesting additional, endocrine, ATX effects.

Hepatocyte ATX expression in CCl4-intoxicated fibrotic livers, leading to increased liver and plasma LPA levels, coincided with aSMA protein expression from HSCs [18], an established marker of their differentiation to myofibroblasts, a central event in disease pathogenesis [98]. *Ex vivo*, LPA promoted cytoskeletal rearrangements, inhibited apoptosis and stimulated aSMA expression in mouse primary HSCs [18], in overall agreement with earlier *in vitro* studies [3,17], confirming that LPA mediates the pathogenic effects of ATX in liver fibrosis.

Pharmacological inhibition of ATX attenuated CCl_4-induced fibrosis

Table 2
In vivo studies with genetically modified mice in animal models of chronic inflammatory disease.

Genetic intervention	Animal model	Effect	Reference (PMID)
Lpar1 ubiquitous deletion	BLM-induced pulmonary fibrosis	Decreased epithelial apoptosis, vascular leak and inhibited fibroblast recruitment	18066075
Enpp2 deletion in macrophages (*LySM*$^{+}$) or bronchial epithelial cells (*CC10*$^{+}$)	BLM-induced pulmonary fibrosis	Decreased vascular leak, inflammatory cell influx, as well as TGFβ and collagen expression	22744859
Lpar2 ubiquitous deletion	BLM-induced pulmonary fibrosis	Decreased epithelial apoptosis, vascular leak and inhibited fibroblast recruitment	23808384
Enpp2 deletion in (*ColVI*$^{+}$) mesenchymal cells (including synovial fibroblasts)	Collagen induced arthritis (CIA)	Lack of synovial inflammation, disease attenuation	22493518
	Transgenic TNF (*hTNF*$^{+/-}$; *Tg197*) mice	Decreased inflammation and synovial hyperplasia	22493518
Lpar1 ubiquitous deletion	Collagen induced arthritis (CIA)	Reduced immune response and skeletal remodeling	23666827
Enpp2 deletion in hepatocytes (Alb^{+})	CCl4-induced liver fibrosis	Disease attenuation	27981605
Enpp2 deletion in adipocytes (Adipoq^{+})	HFD-induced NASH	Decreased steatosis	30730895
Transgenic *Enpp2* over expression from hepatocytes (*a1t1*)	CCl4-induced liver fibrosis	Increased collagen deposition and fibrosis	27981605

PMID: PubMed identifier; BLM: bleomycin; CCl4: Carbon tetrachloride; HFD: High-fat diet; NASH: nonalcoholic steatohepatitis.

and HFD-induced NASH (Table 3), suggesting ATX as a therapeutic target; however, opposing results have been also reported (Table 3). Noteworthy, ATX was reported to get inactivated by the bile salt taurourdeoxycholate (TUDCA) [111], an established treatment of PBC, suggesting that TUDCA efficacy could be partly attributed to ATX inhibition.

7. ATX in rheumatoid arthritis (RA)

RA is a chronic autoimmune disease with a high prevalence and a substantial socioeconomic burden, characterized by autoantibodies and synovial chronic inflammation, leading to the destruction of cartilage and bone. TNF, the major pro-inflammatory factor and current therapeutic target in RA, stimulates the activation of synovial fibroblasts (SFs), the main effector cells in disease pathogenesis and the release of many pro-inflammatory factors and tissue remodeling enzymes [112,113].

Increased ATX mRNA was discovered in arthritic mouse SFs isolated from animal models, in the context of large scale expression profiling [114], while ATX was detected in the synovial fluid of RA patients [115]. Thereafter, increased ATX expression was reported in the arthritic synovium of RA patients and animal models [116,117]. On the other hand, different LPA receptors were also reported to be expressed in mouse and human SFs [115–119]; LPAR1 was consistently found highly expressed in the synovium of RA patients [117,118].

TNF was shown to stimulate ATX expression in mouse primary SFs *ex vivo* [116], as also shown in mouse primary hepatocytes *ex vivo* [18] and hepatoma cell lines *in vitro* [120]. TNF-overexpressing mouse primary SFs were also shown to overexpress ATX [116]. TNF treatment of a TNF-driven, chronic inflammatory, polyarthritis model (Tg190; *hTNF*$^{+/-}$) [121] that attenuated disease pathogenesis, also diminished the exuberant ATX expression in this model [116]. Therefore, TNF seems to drive ATX expression in the arthritic joint, adding one more effect to its pleiotropic actions.

Conditional genetic deletion of *Enpp2* in *ColVI*$^{+}$ mesenchymal cells including SFs, attenuated disease development both in the transgenic *hTNF* $^{\pm}$ model, as well as in the autoimmune model of collagen induced arthritis (CIA) [116], establishing a pathogenic autocrine role for ATX expression from arthritic SFs. As in the case of BLM-induced pulmonary fibrosis, ubiquitous genetic deletion of *Lpar1,* also attenuated the pathogenesis of collagen induced arthritis (CIA) [117], thus suggesting the ATX/LPA/LPAR1 axis as a major player in arthritic disease pathogenesis.

Notwithstanding the important role of ATX and LPA signaling in skeletal development and pathophysiology [45,46], and the possible profibrotic role of LPA in the arthritic synovium [122], multiple effects of LPA have been reported in SFs. Consistent with its GPCR-mediated major effects, LPA rearranged, via Rho A, the actin cytoskeleton of mouse primary SFs [116], induced their proliferation via Gi, Rho kinase, ERK, JNK, p38 pathways [116,123], stimulated MMP9 expression and promoted adhesion and migration [116]. Besides the autocrine effects of ATX/LPA to synovial fibroblast physiology, LPA has also been reported to stimulate the expression of various pro-inflammatory mediators from SFs, most notably IL-6 and IL-8 [115,116,123–125], thus stimulating immune responses. LPA has been reported to promote T cell recruitment in the arthritic synovium [126] and to regulate lymphocyte trafficking and macrophage activation.

Taken together, existing results suggest that upon chronic inflammation of the joints, TNF and the inflammatory milieu stimulates ATX expression from SFs leading to their autoactivation and promotion of their effector functions, via LPA/LPAR1, culminating in the pathogenesis of arthritis. Accordingly, pharmaceutical targeting of the ATX/LPA/LPAR1 axis attenuated disease development in animal models (Table 3). Given the suggested synergy and interplay of LPA with TNF, and the MAPK pathways that both activate [116,125], ATX inhibition could be useful as an adjuvant therapy to current a-TNF treatments, to increase efficiency and reduce dosage. Furthermore, and due to the suggested role of ATX/LPA in skeletal remodeling [45,46] and neuropathic pain [44] respectively, ATX inhibition could be additionally useful for preventing bone erosion in RA [127] or to alleviate joint neuropathic pain [128].

8. Clinical trials targeting ATX

In summary, human correlational data as well as genetic and pharmacological studies in mice (summarized in Tables 1–3 respectively), supported by numerous *in vitro* studies, suggest ATX and LPA signaling as a major multi-faceted player in chronic inflammation and as a possible therapeutic target in different diseases. The list of chronic inflammatory diseases where the ATX/LPA axis is suggested to participate continues to expand, now including kidney fibrosis [129,130], multiple sclerosis [13], Alzheimer's disease [131] and colitis [132]. Therefore, many different ATX inhibitors are being synthesized and tested in various disease animal models [133,134], including IPF, CLDs and RA (Table 3). It should be noted that very few opposing results have been also reported with different ATX inhibitors (Table 3), that can only be attributed to compound characteristics and to animal model differences.

Inducible genetic deletion of ATX in adult mice, resulting in a systemic ~80% decrease of LPA levels, or potent long term enzymatic inhibition, did not result to any gross pathophysiological effects, suggesting that the bulk of ATX activity is dispensable for adult life and

Table 3
In vivo pharmacological studies.

Compound (route; dose)	*In vivo* model	Effect	Target	Reference (PMID)
GWJ-A-23 (IP; 10 mg/kg; on alternate days for 14 days)	BLM-induced pulmonary fibrosis	Attenuated inflammation and fibrosis	ATX	22744859
RB014 aptamer (IN; 20 μg/per mouse; 3 times per week for 10 days)	BLM-induced pulmonary fibrosis	Disease attenuation	ATX	27043297
PAT-048 (PO; 20 mg/kg; once daily for 14 days)	BLM-induced pulmonary fibrosis	No effect	ATX	27006447
GLPG1690 (IN; 30 mg/kg; bid for 21days)	BLM-induced pulmonary fibrosis	Reduced collagen deposition	ATX	28414242
PF8380 (PO; 120 mg/kg; bid for 15 days)	BLM-induced pulmonary fibrosis	Disease attenuation	ATX	30201409
PF8380 (PO; 30 mg/kg; bid for 26 days)	Orthotopic lung transplant model	Decreased lung allograft fibrosis	ATX	28240604
AM966 (PO; 10 mg/kg; bid for 3 days)	3d BLM-induced pulmonary fibrosis	Disease attenuation	LPAR1	20649573
AM095 (PO; 30 mg/kg; bid for 26 days)	Orthotopic lung transplant model	Decreases lung allograft fibrosis	LPAR1	28240604
AM095 (PO; 200 mg/kg; bid for 15 days)	BLM-induced pulmonary fibrosis	Disease attenuation	LPAR1	30201409
BrP-LPA (IP; 10 mg/kg; thrice a week for 26 days)	Collagen Induced Arthritis (CIA)	Reduced inflammation and synovial hyperplasia	ATX & LPARs	23923032
LA-01 (PO, 200 mg/kg/day, bid)	Collagen Induced Arthritis (CIA)	Significant inhibition of clinical arthritis	LPAR1	23666827
Ki 6425 (IP; 20 mg/kg; at days 0, 1, 2, 3)	K/BxN serum-transferred arthritis	Reduction of synovial inflammation, cartilage damage and bone erosion	LPAR1/3	23486415
BMP22 (IP; 1 mg/kg/day; daily for 14 days)	Transgenic TNF (*hTNF*$^{+/-}$; *Tg197*) mice	Significantly reduced bone erosion	ATX	31162832
PF8380 (PO; 120 mg/kg; bid for 26 days)	Collagen Induced Arthritis (CIA)	Disease attenuation	ATX	*
AM095 (PO; 200 mg/kg; bid for 26 days)	Collagen Induced Arthritis (CIA)	Disease attenuation	LPAR1	*
PF8380 (IP; 30 mg/kg; bid for 4 weeks)	CCl4-induced liver fibrosis	Disease attenuation	ATX	27981605
Ex_31 (PO; 15 mg/kg; bid for 4 weeks)	CCl4-induced liver fibrosis in rats HFD-induced NASH in rats	No effect on biomarkers of liver function, inflammation, or fibrosis	ATX	29197066
PAT-505 (IP; 30 mg/kg; daily for 6 weeks)	Stelic NASH Model	Decreased fibrosis with minor effects in ballooning and inflammation	ATX	27754931
PAT-505 (IP; 30 mg/kg; daily for 7 weeks)	HFD-induced NASH	Reduced liver fibrosis with no significant effect on steatosis, ballooning, or inflammation	ATX	27754931

IP: intraperitoneal; PO: Per Os (orally); IN; intranasally; IV: intravenous; SC: subcutaneous; IC: intracardiac; IN: Intranasally; bid: twice a day; BLM: bleomycin; CCl4: Carbon tetrachloride; HFD: High-fat diet; NASH: nonalcoholic steatohepatitis; *: unpublished data.

that ATX is a safe therapeutic target [135]. Accordingly, in a phase 1 randomized clinical trial (NCT02179502) with GLPG1690, a potent and orally bioavailable ATX inhibitor [136], ATX inhibition was reported to be well tolerated [137].

Among the different indications for the possible therapeutic use of ATX inhibitors, idiopathic pulmonary fibrosis is a disease with a dismal prognosis that presents with an unmet medical need. In a phase 2a randomized placebo-controlled trial (NCT02738801), ATX inhibition with GLPG1690 was shown to be safe and well tolerated, supporting further development of GLPG1690 and ATX inhibition as a novel treatment for IPF [138]. Two identically designed, phase III, randomized, double-blind, placebo-controlled, parallel-group clinical trials, (ISABELA 1 and 2; NCT03711162; NCT03733444) for ATX inhibition with GLPG1690, on top of standard of care (nintedanib or pirfenidone), were initiated in November 2018 [139].

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