Lysophosphatidic acid (LPA) is a ubiquitous lysophospholipid and one of the main membrane-derived lipid signaling molecules. LPA acts as an autocrine/paracrine messenger through at least six G protein-coupled receptors (GPCRs), known as LPA1–6, to induce various cellular processes including wound healing, differentiation, proliferation, migration, and survival. LPA receptors and autotaxin (ATX), a secreted phosphodiesterase that produces this phospholipid, are overexpressed in many cancers and impact several features of the disease, including cancer-related inflammation, development, and progression. Many ongoing studies aim to understand ATX-LPA axis signaling in cancer and its potential as a therapeutic target. In this review, we discuss the evidence linking LPA signaling to cancer-related inflammation and its impact on cancer progression.

1. Introduction
Lysophosphatidic acid (LPA) consists of an acyl chain at the sn-1 (or sn-2) position of a glycerol backbone and a phosphate head group. It is the smallest (molecular weight: 430–480 Da) and the simplest bioactive glycerophospholipid derived from membrane phospholipids [1, 2]. Nevertheless, it is involved in a wide range of activities, from phospholipid synthesis to a number of physiological responses as a lipid mediator [3]. LPA activates at least six G-coupled protein receptors (LPA1–6) stimulating different signaling pathways through heterotrimeric G proteins such as Gαi0, G12/13, Gq/11, and Gε. The outcome of LPA signaling is dependent on cellular context and impacts on biological processes such as wound healing, differentiation, neurogenesis, and survival, to name a few [4]. Due to its small structure, LPA is water soluble and concentrations > 5 μM have been reported in serum; concentrations < 1 μM have been found in other biofluids such as plasma, saliva, follicular fluid, cerebrospinal fluid, and malignant effusions [5–7]. It is known that ATX-LPA signaling increases during wound healing, and both are produced and detected in blister fluids, where they mediate platelet aggregation and skin reepithelization [8]. During this process, ATX-LPA signaling induces production of proinflammatory cytokines. Therefore, aberrant activation of this axis promotes an inappropriate immune response that leads to a proinflammatory state in pathologies like cancer [9].

2. Lysophosphatidic Acid Synthesis and Metabolism
LPA is a membrane-derived lysophospholipid from phosphatidylycholine (PC), phosphatidylserine (PS), and phosphatidylethanolamine (PE) [7]. Therefore, several species can be found, differing only in the length and saturation of the acyl or alkyl fatty acid chain [7, 10]. The most abundant plasma LPA species are 18:2 > 18:1 > 18:0 > 16:0 > 20:4 with an acyl group [11, 12]. Although acyl-LPA 18:2 is the most numerous species, acyl-LPA 18:1 is the most frequently used in current research [13].

There are two major pathways for LPA production (Figure 1(a)). The main pathway is the cleavage of membrane phospholipids into lysophospholipids by the removal of a
fatty acid chain by phospholipase A (PLA1 or PLA2). Subsequently, ATX cleaves the head group (choline, ethanolamine, or serine) on the lysophospholipids and turns them into LPA [14]. ATX (also known as ENPP2) is a 125 kDa-secreted enzyme from the family of ectonucleotide pyrophosphatases/phosphodiesterases (reviewed by [15]) located on Chr8q24 [16]. Among the seven members of this family, ATX is a unique enzyme that shows lysophospholipase D activity.
acyl-LPA, specifically 42 kDa and di- transmembrane domain receptors that range from 39 to 50 kDa [30, 31]. All LPA receptors are rhodopsin-like, with seven transmembrane helices, and they differ in their tissue distribution and downstream effectors [7]. According to their homology, they are two LPA receptor families: the endothelial differentiation gene (EDG) family and the non-EDG family [32, 33]. In addition to homology, they differ in their activation by different LPA species (Figure 2). Although acyl-LPA is the most abundant species, the EDG family is more potently stimulated by acyl-LPA (LPA<sub>1</sub>) and LPA<sub>2</sub> preferentially binds to 2-acyl-LPA. The non-EDG family member LPA<sub>3</sub> is more potently stimulated by alkyl-LPA and LPA<sub>3</sub> by 2-acyl-LPA, specifically [33]. These differences show that a wide range of physiological effects is modulated through these receptors and LPA species in a context and cell type-dependent manner.

3.1. Endothelial Differentiation Gene Family. In 1996, LPA<sub>1</sub> was the first receptor to be identified and it is the best studied to date. Hecht et al. [35] described a neuroblast cell line overexpressing the ventricular zone gene-1 receptor (Vgz-1), to which LPA binds specifically to induce cell rounding and activation of G<sub>αi</sub>. Also known as EDG-2, Vgz-1 was later renamed LPA<sub>1</sub>. Right after its discovery, two other orphan receptors, LPA<sub>2</sub> and LPA<sub>3</sub>, were identified based on their homology to LPA<sub>1</sub> [36–38].

LPA<sub>1</sub> is a 41 kDa protein of 364 amino acids located in Chr9q31.3 and consists of at least 5 exons [30, 31]. This receptor couples with and activates 3 types of G protein, G<sub>αi/0</sub>, G<sub>αq/11</sub>, and G<sub>α12/13</sub>, which initiate downstream signaling through PI3K/AKT, Rho, MAPK, and PLC (Figure 1(b)). These pathways are involved in several cellular processes, including cell proliferation and survival, adhesion, migration, AC inhibition, and Ca<sup>2+</sup> mobilization [31, 39]. It is widely expressed in most tissues such as brain, uterus, testis, lung, small intestine, heart, stomach, kidney, spleen, thymus, and skeletal muscle at different developmental stages with a variable expression, particularly in the central nervous system (CNS) [36, 39], where, during development, LPA<sub>1</sub> is found in the ventricular zone, superficial marginal zone, and meninges. After birth, LPA<sub>1</sub> expression is reduced in the aforementioned areas and continues in oligodendrocytes, particularly during myelination, as well as in astrocytes, where it elicits a wide range of processes (reviewed by [40]). Targeted deletion of Lpar1<sup>−/−</sup> showed a 50% of perinatal lethality related to an impaired suckling behavior probably due to defective olfaction. Surviving mice showed craniofacial malformations and reduced body size [41]. Additionally, LPA<sub>1</sub> has been closely related to the induction of neuropathic pain due to nerve injury via LPA<sub>1</sub>/RhoA/rock-mediated demyelination with a subsequent loss of the structural and functional integrity of neurons, as discussed elsewhere [42].

LPA<sub>1</sub> receptor (EDG-4) has a ~50–60% homology to LPA<sub>1</sub>, with an estimated mass of 39 kDa and 348 amino acids [36]. Located on Chr19p12, it consists of 3 exons in both humans and mice [30, 39]. LPA<sub>2</sub> couples to the same G proteins as LPA<sub>1</sub> (Figure 1(b)): G<sub>αi/0</sub>, G<sub>αq/11</sub>, and G<sub>α12/13</sub> [36, 39]; therefore, it can similarly activate downstream signaling but, unlike LPA<sub>1</sub>, can also promote migration through the focal adhesion molecule TRIP6 [43, 44]. LPA<sub>2</sub> activation is associated with survival and migration. Compared with LPA<sub>1</sub>, its expression is more diffuse during development, more restricted in adults, and with high expression in leukocytes and testis in humans and in kidney, uterus, and testis in mice [36, 39, 45]. LPA<sub>2</sub> knockout mice are mostly normal, suggesting a possible functional redundancy in relation to LPA<sub>1</sub>. A Lpar1<sup>−/−</sup> and Lpar2<sup>−/−</sup> model has also been evaluated [46]. In this model, Lpar1<sup>−/−</sup> phenotype predominated with 50% perinatal lethality, cranial malformations, and reduced body size, but it also exhibited frontal hematomas [46].

LPA<sub>3</sub> receptor (EDG-7) contains 3 exons, has 353 amino acids, and a 40 kDa-estimated mass [37, 38]. This receptor has 52% and 48% homology with LPA<sub>1</sub> and LPA<sub>2</sub>, respectively, and is located on Chr1p22.3-p31.1 [30, 38, 39]. LPA<sub>3</sub> couples to G proteins, G<sub>αi/0</sub> and G<sub>α12/13</sub> (Figure 1(b)), and therefore mediates downstream activation of MAPK, PLC, and inactivation of AC [47]. It has been reported that this receptor is more potent by 2-acyl-LPA with unsaturated fatty acids [2]. In humans, LPA<sub>3</sub> is expressed in heart, lung, pancreas, prostate, testis, ovaries, and brain [37]. In mice, it is expressed in testis, kidney, lung,
intestine, and moderately, small intestine [39]. Functional deletion of LPA3 in female mice showed delayed and defective embryo implantation through the downregulation of cyclooxygenase-2 (COX-2) and reduced levels of prostaglandins, which are essential for this process [48]. In deficient LPA1–3 male mice, an independent of testosterone signaling reduced sperm count and mating activity was found [49]. This evidence suggests the role of LPA3 in reproductive functions.

3.2. Nonendothelial Differentiation Gene Family. In 2003, the first LPA receptors structurally distant from the EDG receptor family were described [50]. The orphan GPCR P2Y9/GPR23 has only 20–24% homology with LPA1–3, but it specifically binds to LPA. Its signaling promotes an increase in intracellular Ca2+ concentration and adenyl cyclase activity in “LPA receptor-null” cells exogenously expressing P2Y9 [50]. Soon, LPA5 and LPA6 description followed [51–55].

LPA4 (P2Y9/GPR23) is encoded by 1 exon containing 370 amino acids with a 42 kDa mass [30, 50, 56]. Located on ChrXq21.1, it was the first to be described that couples to four G proteins: Gαi0, Gα11/q, Gα12/13, and Gαs (Figure 1(b)) [57]. LPA4 signaling promotes Rho-mediated neurite retraction and stresses fiber formation, Ca2+ mobilization, and regulation of cAMP concentration [57]. In humans, LPA4 expression is high in ovaries, moderated in thymus and pancreas, and low in brain, heart, small intestine, testis, prostate, colon, and spleen [13, 50]. In mice, it is expressed in heart, ovaries, thymus, skin, and developing brain [57, 58]. Lpar4−/− mice showed no apparent abnormality, but there was a 30% lethality, probably due to blood vessel defects during embryogenesis [58, 59].

LPA5 (GPR92) is a 41 kDa protein consisting of 372 amino acids coded in an intronless open reading frame [51, 52]. This receptor is located on Chr12p13.31 and has a 35% homology with LPA4 [51, 52]. LPA5 couples

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**Figure 2: LPA species.** LPA is derived from phospholipids with different lengths and saturations. (a) 18 carbon LPA species with an acyl group in sn-1 position and one saturation are the most potent activator of the LPA1 and LPA2 receptors [7]. (b) Acyl LPA with 18 carbons, one saturation, and the fatty acid chain in sn-2 position are the most potent activator of LPA3 and LPA6 [2, 34]. (c) An alkyl-LPA species with 16 carbons and no saturation are the most potent activator of LPA5 receptor [33].
Ca\(^{2+}\) mobilization, inositol phosphate production, neurite growth has been related to hair growth since a mutation of stomach, and small and large intestine [54]. In humans, it is found in rats LPA, rather than 1-acyl-LPA [53]. This receptor has been implicated in alopecia-causing disorder [55]. It was found in patients with hypotrichosis simplex, an autosomal recessive hair migratory disorder [51, 52]. Lpar5\(^{-/-}\) mice have no apparent phenotypic defects but show a reduced pain sensitivity, faster recovery from inflammation, and reduction in social exploration [61, 62]. They also exhibit nocturnal hyperactivity and anxiety compared to Lpar5\(^{+/+}\) mice [61]. Null mice were also protected from developing neuropathic pain by a mechanism different from LPA4 [62].

LPA6 (P2Y5) is the most recently identified LPA receptor and the last accepted by the IUPHAR Nomenclature Committee in 2010 [31, 53, 54]. It is a 344-amino acid protein with an estimated mass of 39 kDa [30]. Regarding homology with LPA4 [50], it is the closest receptor and is located on Chr13q14 [30, 55]. LPA6 couples to G\(\alpha_{12/13}\) and G\(\alpha_{11i}\) (Figure 1(b)), by which a decrease in cAMP, Rho-dependent morphological changes, Ca\(^{2+}\) mobilization, and MAPK activation are mediated [53, 54]. It has also been reported that LPA6 is preferentially activated by 2-acyl-LPA, rather than 1-acyl-LPA [53]. This receptor has been found in rats’ brain, heart, lung, kidney, pancreas, liver, stomach, and small and large intestine [54]. In humans, it has been related to hair growth since a mutation of LPAR6 was found in patients with hypotrichosis simplex, an alopecia-causing disorder [55].

3.3. EDG and Non-EDG Receptor Effects in Cancer. Extensive evidence demonstrates that the receptors from the EDG family promote tumor progression in a wide variety of cancers by enhancing proliferation, survival, migration, and invasion [7]. Conversely, evidence shows that members from the non-EDG family have the opposite effect.

Reconstitution of Lpar4 in mouse embryonic fibroblasts derived from Lpar4\(^{-/-}\) mice reduces cell motility due to an LPA-induced decrease in Rac activation [58]. Also, LPA4 expression in colon cancer cells (DLD1 and HTC116) suppresses cell migration and invasion compared to null-LPA4 cells [58, 63]. Similarly, in rat sarcoma cells, overexpression of Lpar5 significantly reduced motility and suppressed MMP2 activation. On the other hand, Lpar5 knockdown induced the opposite effect [64]. In B16F10 mouse melanoma cells, LPA3 reduced migration through a cAMP/PKA-dependent pathway and induced chemorepulsion instead of attraction via LPA [65]. Additionally, in colon cancer cells, lines DLD1, and HCT116, LPA4 expression significantly reduced cell growth and motility [63]. In rat lung adenocarcinoma, loss of LPA3 due to methylation of the promoter enhances tumor progression by increasing invasion, suggesting a protective role of LPA3 in this neoplasia [66]. By contrast, in human fibrosarcoma, LPA4 was shown to increase cAMP levels and subsequently activate Rac1 to induce invadopodia, a process directly correlated with invasion and metastasis [67]. Additionally, in rat lung carcinoma, LPA4 is highly expressed due to unmethylation of the promoter, and cells expressing only LPA4 showed enhanced proliferation, migration, and invasion [68]. Moreover, hepatocellular carcinoma (HCC) cells overexpressing LPA4 sustain an increase in tumor growth, migration, and invasion. Moreover, LPA4 expression was associated with a worse clinical outcome in these patients [69].

In brief, LPA receptors can have homologous and antagonistic effects depending on the tumor. Therefore, they should be studied in a cancer-specific context to better evaluate their role in tumor development and progression, as well as their potential therapeutic value.

4. Autotaxin-LPA Axis in Cancer-Related Inflammation

Since the 19th century, an association between inflammation and cancer was proposed [70]. Inflammatory components are often present in most types of cancer, such as white blood cells, tumor-associated macrophages, and proinflammatory ILs [70, 71]. In several cases, inflammation can predispose individuals to certain types of cancer, including cervical, gastric, colon, hepatic, breast, lung, ovarian, prostate, and thyroid cancer [72–81]. There is also evidence that the use of nonsteroidal anti-inflammatory drugs can reduce the risk of developing colon and breast cancer and reduce the related mortality, as discussed elsewhere [82, 83].

In general, two mechanisms have been proposed to link inflammation and cancer. In the intrinsic pathway, genetic events promoting development initiate the expression of inflammation-related circuits leading to an inflammatory microenvironment. Conversely, in the extrinsic pathway, inflammatory conditions facilitate cancer development. In both cases, a cancer-related inflammation (CRI) is induced and it is proposed as a tumor-enabling characteristic and the seventh hallmark of cancer [71]. CRI enables unlimited replicative potential, independence of growth factors, resistance to growth inhibition, escape of cell death, enhanced angiogenesis, tumor extravasation, and metastasis [84]. Therefore, understanding key components of inflammation is important for better therapeutics in cancer and other diseases.

The ATX-LPA axis is involved in wound healing response, where it induces platelet aggregation, lymphocyte homing, cytokine production, keratinocyte migration, proliferation, and differentiation under physiological conditions [85]. When acute inflammation becomes chronic in unpaired homeostasis, ATX-LPA signaling induces an augmented cytokine production and lymphocyte infiltration, aggravating the inflammation in conditions such as asthma, pulmonary fibrosis, and rheumatoid arthritis, to name a few [86]. In a cancer context, it also promotes cell survival, proliferation, migration, invasion, and angiogenesis, enhancing its progression in a state similar to a “wound that never heals” [84, 87].

4.1. Lung. ATX-LPA axis has been studied in airway inflammation where protein kinase C\(\delta\) (PKC\(\delta\)) mediates...
LPA-induced NFκB transcription and IL-8 secretion in human bronchial epithelial cells (HBEpCs) [88]; LPA activation of PKCδ/NFκB and IL-8 production were inhibited by rottlerin (a nonspecific PKCδ inhibitor) and by an overexpression of dominant-negative PKCδ. In vivo LPA administration in mice leads to increased levels of a murine homolog of IL-8 and of neutrophils in the bronchoalveolar fluid [88]. Moreover, LPA signaling induces EGFR transactivation via Lyn kinase, from Src kinase family, to promote matrix metalloprotease (MMP) secretion as well as IL-8 [89]. Additionally, activation of the signal transducers and activators of the transcription 3 (STAT3) in alveolar epithelial cells during host defense promotes inflammation and spontaneous lung cancer [90]. Through these signaling cascades, a chronic inflammation is pursued and could lead to malignant transformation. In lung cancer, inhibition of ATX-LPA axis reduced cell migration, invasion, and vascularization in a 3-D lung cancer xenograft model [91]. There is evidence that ATX is highly expressed in poorer differentiated lung carcinomas, particularly in tumor-adjecent B lymphocytes [92] and that LPA₄ may play a key role in the progression of these carcinomas [68], while LPA₃ could have a protective role [66]. Furthermore, LPA and other phospholipid levels are upregulated as a side effect of chemotherap and radiotherapy, inducing a prometastatic microenvironment in lung cancer [93]. Interestingly, LPA did not induce proliferation nor survival in these cells, but rather an increase in motility, adhesion to bone marrow stroma, and enhanced secretion of ATP, another potent chemokinetic factor, from stroma cells [93]. Together, evidence suggests a significant role of ATX-LPA axis in inflammation and lung cancer through the increase of proinflammatory cytokines.

4.2. Breast. In breast cancer (BCa), the ATX-LPA axis induces inflammation and tumor formation in the mammary gland through LPA₁₋₃ and high ATX expression, which is produced in the adjacent mammary adipose tissue rather than actual cancer cells [94, 95]. Individual overexpression of each of the EDG family receptors, but especially of LPA₂, induced a high frequency of late-onset, estrogen receptor (ER) positive, and invasive and metastatic mammary cancer [94]. Moreover, bone metastases are frequent in BCa; ATX expression in these tumors can control the progression of osteolytic bone metastases in vivo through the procoagulant activity of BCa cells that induce platelet-derived LPA [96].

ATX-LPA axis is a strong inducer of inflammatory mediators like IL-8, IL-6, TNF-α, and growth factors such as the vascular endothelial growth factor (VEGF) and the granulocyte colony-stimulating factor (G-CSF) [95]. Some molecules (IL-8 and VEGF) were detected earlier than tumorigenesis in vivo [94]. Inhibition of ATX induced a two-fold reduction in at least 20 of these inflammatory mediators in the tumor-adjecent mammary adipose tissue-reducing inflammation and tumorigenesis [95]. Additionally, expression of LPA₁₋₃ increased phosphorylation of STAT3, STAT5, NFκB and AFT2, and master inflammatory transcription factors, in mouse mammary carcinomas [94]. Furthermore, cytokines produced in the microenvironment (i.e., IL-6) can activate STAT3 through its receptors inducing an inflammatory loop [97]. Adipose tissue adjacent to breast tumors stimulates autotaxin (ATX) secretion, which increases tumor growth and metastasis [19]. Interestingly, radiotherapy in adipose tissue of rats and humans increased mRNA expression of ATX, multiple inflammatory mediators, and LPA₁₋₂. Such effect could promote LPA signaling and further inflammatory signaling, which in turn could potentially protect cancer cells from subsequent radiation therapy [98]. ATX inhibition reduced the leukocyte infiltration and tumor growth in vivo [95]. All these evidence suggest that chronic inflammation contributes to tumor development in BCa. Controlling inflammation and cancer progression could be achieved by targeting the ATX-LPA axis.

4.3. Ovary. In ovarian cancer (OC), ATX is highly expressed and secreted by cancer cells [99]. Therefore, LPA is present at high concentrations in the ascites fluid of OC patients compared to benign and healthy controls and has been proposed as a potential biomarker [100–102]. LPA acts as a growth factor and prevents apoptosis in OC cells by signaling through redox-dependent activation of ERK, AKT, and NFκB signaling pathways. Inhibiting ROS production blocked LPA/NFκB signaling and cell proliferation [103]. Additionally, LPA has been shown to upregulate the expression of human telomerase reverse transcriptase (hTERT) and telomerase activity in OC cell lines, through a PI3K and HIF-1α-dependent mechanism, enabling replicative immortality [104]. On the other hand, OC cell lines, SKOV-3, and OVCAR3 that expressed increased LPA₁₋₃ receptors showed more invasiveness compared to knockdowns. Moreover, via LPA₂₋₃, OC cells promote production of IL-6, IL-8, and VEGF in vitro [105] and induced urokinase plasminogen activator (uPA) secretion in a MAPK- (p38) and PI3K-dependent mechanism that required Src kinase for optimal MAPK phosphorylation, enhancing OC invasion [106].

4.4. Liver. Liver cirrhosis, a terminal stage of chronic inflammatory and fibrotic liver diseases, and chronic hepatitis C are distinct risk factors for hepatocellular carcinoma (HCC) [107, 108]. Increased serum ATX activity and plasma LPA levels have been found in patients with chronic hepatitis C in association with a histological stage of liver fibrosis [108]. Furthermore, in HCC, ATX is expressed in 89% of tumor tissues, especially in those with cirrhosis or hepatitis C, compared to 20% in normal hepatocytes [109]. Additionally, in HCC cell lines, TNF-α/NFκB pathway, known to contribute to inflammation-associated cancer, was shown to upregulate ATX expression and LPA production. The latter resulted in an increased cellular invasion [109]. Similarly, LPA modulates tumor microenvironment by inducing transdifferentiation of peritumoral fibroblasts to a CAF-like myofibroblastic phenotype which enhances proliferation, migration, and invasion in HCC [110]. Additionally, LPA₆ mediates tumor growth and tumorigenicity by upregulating Pim-3 protooncogene through a STAT3-dependent mechanism [69]. Recently, human cirrhosis regulatory gene modules were identified through a transcriptome meta-analysis [107]. This analysis provides an overview of a molecular dysregulation common to a wide range of liver disease.
Table 1: Targeting the ATX-LPA axis in cancer and inflammation.

| Name       | Target       | Mechanism of action                                                                 | Phase   | Indication/model | Reference          |
|------------|--------------|-------------------------------------------------------------------------------------|---------|-----------------|--------------------|
| HA130      | ATX          | It binds to the active site of ATX (T210). IC$_{50}$ = 28 nM in vitro               | Preclinical | Melanoma        | [25]               |
| PF-8380    | ATX          | Direct binding to ATX. Inhibits lysoPLD activity. IC$_{50}$ = 2.8 nM isolated ATX  | Preclinical | (i) Inflammation | [133–135]         |
|            |              | IC$_{50}$ = 101 nM in vivo                                                        |         | (ii) Glioblastoma|                   |
| ONO-8430506| ATX          | Direct binding to ATX. Inhibits lysoPLD activity. IC$_{50}$ = 4.5 nM isolated ATX  | Preclinical | (i) Breast cancer| [19, 28, 121, 136] |
|            |              | IC$_{50}$ = 4.1–11.6 nM in vivo                                                   |         | (ii) BCa metastasis|                   |
|            |              |                                                                                   |         | (iii) Thyroid cancer|                 |
| GLPG1690   | ATX          | Binding to the hydrophobic pocket and hydrophobic channel of the protein. IC$_{50}$ = 131 nM in vitro | Phase II | Idiopathic pulmonary fibrosis | [137, 138] |
| BMS-986020 | LPA$_1$      | Inhibits signaling by LPA$_1$                                                     | Phase II | Idiopathic pulmonary fibrosis | [139, 140] |
| SAR100842  | LPA$_1$      | LPA$_1$ antagonist                                                                   | Phase II | Systemic sclerosis | [141]             |
| BrP-LPA    | ATX, LPA$_1$, | Direct binding to ATX. Inhibits lysoPLD activity. IC$_{50}$ = 600 nM ex vivo      | Preclinical | (i) Rheumatoid arthritis| [142–145]       |
|            | LPA$_2$,     |                                                                                   |         | (ii) Breast cancer|                   |
|            | LPA$_3$,     |                                                                                   |         | (iii) Pancreatic cancer|                 |
|            | LPA$_4$,     |                                                                                   |         | (iv) Glioma      |                   |
|            | LPA$_5$      |                                                                                   |         |                  |                   |

etioologies in which the ATX-LPA axis is a central regulator [107]. This study marks a great breakthrough in the area and provides a promising target for HCC chemoprevention through this axis; mainly due to the compounds of ongoing clinical trials on idiopathic pulmonary fibrosis and systemic sclerosis (Table 1). If approved, they could be tested as preventive therapy in cirrhosis patients and as adjuvant therapy in HCC [107, 111].

4.5. Colon. In human colorectal cancer (CC), expression of LPA$_1$ and LPA$_2$ is increased compared to normal mucosa. Conversely, LPA$_3$ has a low expression in malignant tissues [112]. Evidence suggests a probable role of LPA$_{1/2}$ receptors in CC. Furthermore, LPA-stimulated proliferation through the MAPK pathway, as well as migration through Rho kinase, and chemoresistance through the PI3K/AKT pathway [113]. Inflammation is an established risk for developing CC. Interestingly, in a colitis-associated mice cancer model, Lpar$_2^{-/-}$ showed a decrease in tumor incidence and in progression to colon adenocarcinomas by reducing proliferation and proinflammatory factors such as monocyte chemoattractant protein-1 (MCP-1) and macrophage migration inhibitory factor (MIF) [114]. The latter affected the infiltration of macrophages to the tumor microenvironment [114]. Moreover, although LPA increased tumor incidence in Apc$^{Min/+}$ mice predisposed to adenomas, in Lpar$_2^{-/-}$ Apc$^{Min/+}$, tumor incidence was reduced by 50% [114, 115]. In addition, the expression levels of KLF5, cyclin D1, c-Myc, and HIF-1α were lower compared to Apc$^{Min/+}$ mice, while β-catenin was primarily cytoplasmic in Lpar$_2^{-/-}$ Apc$^{Min/+}$ mice compared to its nuclear localization in Apc$^{Min/+}$ mice [115]. This evidence suggests an important role of ATX-LPA axis in tumorigenesis derived from colon chronic inflammation.

4.6. Others. Along with cancers previously described, ATX-LPA axis and its signaling pathways have been studied in several other carcinomas such as melanoma, where LPA signaling suppresses antigen receptor signaling, cell activation, and proliferation in C8D T cells that express LPA$_5$, inhibiting immune response [116] and promoting tumorigenesis. In pancreatic cancer, LPA$_1$ and LPA$_3$ promote proliferation, invasion through MMP2 secretion, and activation of focal adhesion kinase (FAK) and Paxillin, as well as drug resistance [117, 118]. In glioblastoma multiforme (GBM), an increased ATX-LPA axis has been described to promote cell proliferation and migration through LPA$_1$ [119]. GBM is also characterized by high levels of inflammatory mediators and activation of AKT and NFκB signaling pathways, although the link between ATX-LPA and inflammation remains to be studied [120]. In thyroid cancer, ATX is highly expressed in papillary thyroid carcinomas compared with benign neoplasm [121]. ATX-LPA axis induces at least 16 inflammatory mediators, including IL1-β, IL6, IL8, G-CSF, and TNF-α in vivo; at the same time, these mediators induce ATX expression and increase LPA levels. Blocking the ATX-LPA axis induced a reduction of inflammatory mediators, tumor volume, and angiogenesis [121]. In renal cell carcinoma, ATX-LPA axis is associated to chemoresistance through LPA$_1$. Coadministration of Ki16425, an LPA$_{1/3}$ antagonist, with sunitinib, a tyrosine kinase inhibitor, prolonged the responsiveness of renal cell carcinoma to sunitinib [122].

So far, the evidence shows that ATX-LPA signaling in cancer is more complex than previously thought. In addition to promoting proliferation, aggressiveness, and metastasis, it induces an enabling inflammatory setting (Figure 3) and contributes to the differentiation of CAFs [123],
leukocyte infiltration [92, 116], angiogenesis [123], and stem cell maintenance [99]; all of them are important components of tumor microenvironment (Figure 4). Thus, the ATX-LPA axis represents a crucial target to reduce CRI and cancer progression.

5. Targeting Autotaxin-LPA Axis for Cancer Therapy

LPA signaling is regulated by ATX activity, LPA receptors, and LPA degradation by LPP1 and LPAAT [125, 126]. In
numerous cancers, ATX protein is overexpressed, leading to increased LPA levels in the tumor microenvironment and peripheral blood [99, 101, 127]. Cancer cells have a higher LPA receptor content on their cell surface compared to normal and benign cells and a downregulated expression of LPPs [128]. Therefore, targeting LPA signaling through these components is currently under study and constantly reviewed [4, 127, 129–132]. In this section, we summarize some of the drugs studied regarding ATX inhibition and LPA receptor antagonism (Table 1).

ATX-LPA axis has been shown to induce chemoresistance by upregulating antioxidant genes, multidrug-resistant transporters (ABCC1, ABCG2, ABCC2, and ABCC3), aldehyde dehydrogenase 1 (ALDH1), and stem cell maintenance [99, 136]. Additionally, ATX is among the top 40 most upregulated genes in metastatic cancer [146]. Therefore, inhibition of the axis has shown great results as adjuvant therapy to enhance both chemo- and radiotherapy in vitro and in vivo, as well as tumor growth reduction. Additionally, as we described, CRI is an enabling setting for tumor development. We suggest that a strategy to be considered regarding the ATX-LPA axis in CRI should be a multitarget approach, where both proinflammatory cytokines and ATX-LPA are taken into consideration for better outcomes.

Currently, drugs of ongoing clinical trials are for non-cancer diseases; nevertheless, once approved, they could be tested in various cancers. Meanwhile, improvement of physiological and pathological knowledge regarding signal transduction by this axis will lead to the development of more specific therapeutic drugs to better target this signaling cascade.
6. Conclusions

The ATX-LPA signaling pathway is physiologically relevant during development and adulthood. Dysregulation of this axis is linked to several pathologies, including inflammation-related conditions such as rheumatoid arthritis, fibrosis, neuropathic pain, and cancer. In cancer, it has a major involvement in key components of the microenvironment, including leukocyte infiltration, angiogenesis, and decreased immune response. Interestingly, this axis has been shown to enhance proinflammatory pathways, crosstalk, and positive loops. Therefore, including leukocyte involvement in key components of the microenvironment, neuropahtic pain, and cancer. In cancer, it has a major resistance to cancer treatments. Recent evidence in cirrhosis patients point to this axis as a key regulator in HCC tumor genesis, providing a very interesting potential target for cancer prevention.

As we wait for ATX-LPA inhibitors to move from preclinical into clinical trials, further investigation is needed regarding this complex signaling pathway to achieve more efficient therapeutics in cancer and other ATX-LPA axis-related pathologies.

Abbreviations

LPA: Lysophosphatidic acid
GPCR: G protein-coupled receptor
ATX: Autotaxin
PC: Phosphatidylcholine
PS: Phosphatidyserine
PE: Phosphatidylethanolamine
PLA1: Phospholipase A1
PLA2: Phospholipase A2
LPC: Lysophosphatidylcholine
PA: Phosphatidic acid
PLD: Phospholipase D
sPLA2: Secreted phospholipase A2
LPP1: Lipid phosphate phosphohydrolase type 1
MAG: Monoacylglycerol
LPAAT: Lysophosphatidic acid acyltransferase
LPE: Lysophosphatidylethanolamine
LPS: Lysophosphatidylserine
cPLA2: Cytosolic phospholipase A2
AC: Adenyl cyclase
EDG family: Endothelial differentiation gene family
Vgz-1: Ventricular zone gene-1
CNS: Central nervous system
COX-2: Cyclooxygenase-2
HCC: Hepatocellular carcinoma
CRI: Cancer-related inflammation
PKC: Protein kinase C
HBEpC: Human bronchial epithelial cells
MMP: Matrix metalloprotease
Stat: Signal transducers and activators of the transcription

BCa: Breast cancer
ER: Estrogen receptor
IL: Interleukin
TNF-α: Tumor necrosis factor α
VEGF: Vascular endothelial growth factor
G-CSF: Granulocyte colony-stimulating factor
NFkB: Nuclear factor kappa-light-chain-enhancer of activated B cells
ATF2: Activating transcription factor 2
OC: Ovarian cancer
ROS: Reactive oxygen species
hTERT: Human telomerase reverse transcriptase
HIF-1α: Hypoxia-inducible factor-1α
uPA: Urokinase plasminogen activator
MCP-1: Monocyte chemoattractant protein-1
MIF: Macrophage migration inhibitory factor
KLF5: Krüppel-like factor 5
FAK: Focal adhesion kinase
GBM: Glioblastoma multiforme
CAF: Cancer-associated fibroblast
EGFR: Epidermal growth factor receptor
ECM: Extracellular matrix
ALDH1: Aldehyde dehydrogenase 1.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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