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Review Article

Autotaxin-Lysophosphatidic Acid: From Inflammation to Cancer Development

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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 LPA_{1-6}, 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 (LPA_{1-6}) stimulating different signaling pathways through heterotrimeric G proteins such as $G_{i/0}$, $G_{12/13}$, $G_{q/11}$, and G_s. 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 $> 5\,\mu$M have been reported in serum; concentrations $< 1\,\mu$M 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 phosphatidylcholine (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

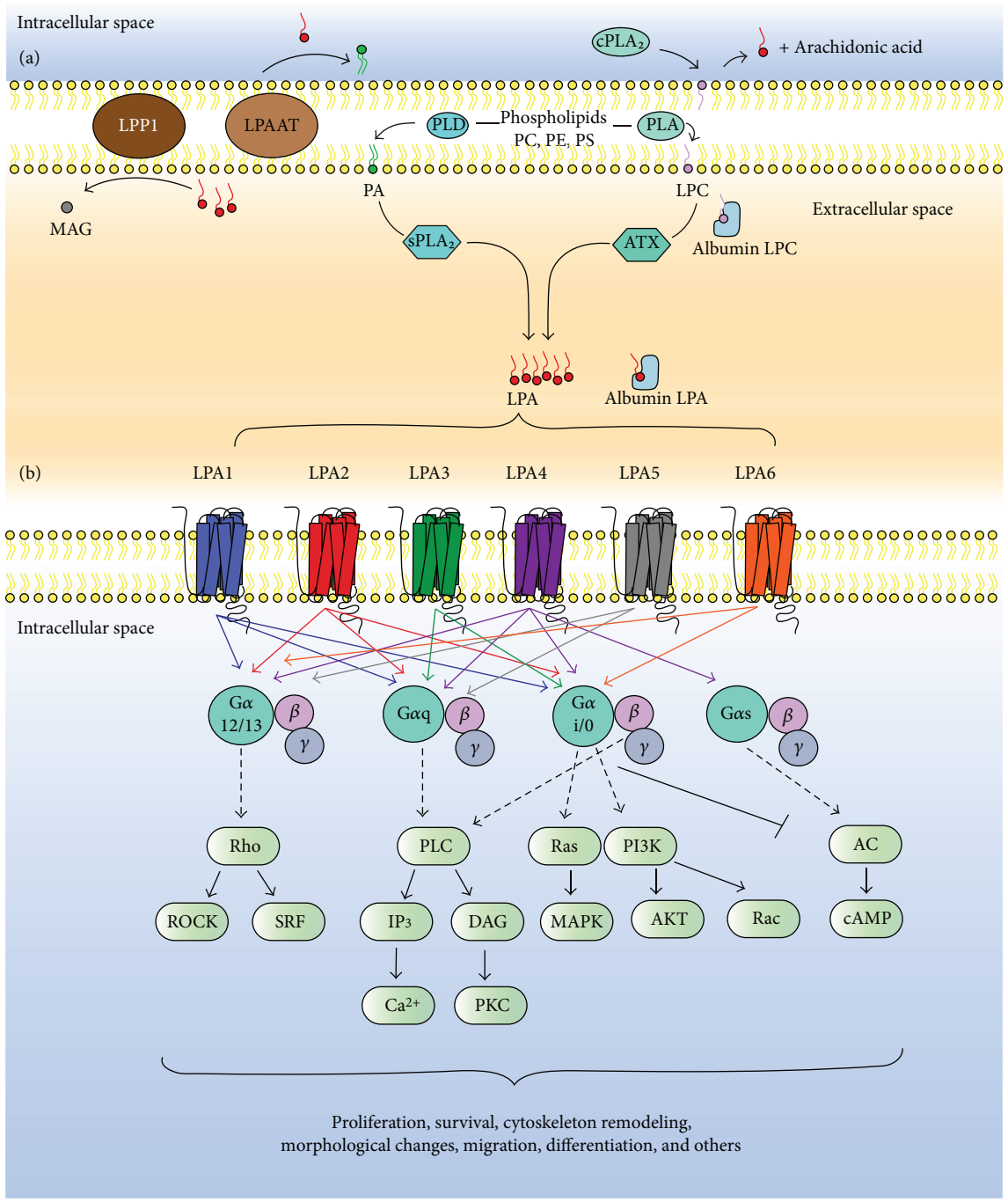

Figure 1: LPA production, metabolism, and signaling. (a) LPA species are derived from membrane phospholipids. PLA removes a fatty acid chain from PC, PE, or PS converting them into lysophospholipids. Afterwards, ATX removes the head group from LPC < LPE < LPS and produces LPA. LPC can derive from cell membrane or circulating LPC bound to albumin. LPA can also be produced intracellularly by cPLA2 from LPC producing LPA and arachidonic acid. On the other hand, PLD can remove the head group from membrane phospholipids and produce PA. Then, sPLA2 removes a fatty acid chain producing LPA. Two enzymes metabolize LPA, LPP1 in the outer leaflet of the membrane hydrolyzes LPA into MAG, and LPAAT transfers an acyl chain to LPA in the inner leaflet of the membrane producing PA. (b) LPA signals through at least six GPCRS (LPA_{1-6}) that couple to different Gα proteins to elicit activation of Rho, PLC, Ras, PI3K, and adenylyl cyclase (AC) and mediate diverse processes that are cell and context dependent. This figure is reproduced from Blaho and Hla [29] (under the Creative Commons Attribution License/public domain).

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

[17, 18]. This enzyme produces most of the extracellular LPA. *Enpp2*$^{+/-}$ mice and inhibitors targeting ATX decrease LPA plasma concentration by >50% [19–22]. ATX generates LPA from plasma membrane phospholipids and from circulating lysophosphatidylcholine (LPC) bound to albumin [23]. ATX is essential for development since *Enpp2*$^{-/-}$ is lethal at embryonic day 9.5–10.5, with marked vascular and neural tube defects [20, 21]. ATX is also important in adipogenesis since it is upregulated during preadipocyte differentiation to adipocytes and secreted into circulation by the adipose tissue [24].

A second, less common, route of LPA production is the cleavage of phospholipids into phosphatidic acid (PA) by phospholipase D (PLD) at the cell surface. PA is then hydrolyzed in the outer leaflet of the plasma membrane by secreted PLA2 (sPLA2) releasing LPA to the microenvironment [15].

LPA turns over with a half-life of about 3 min in the circulation [25]. Therefore, its main effects are autocrine and paracrine when bound to albumin [10]. LPA turnover is regulated by ATX activity and LPA degradation by lipid phosphate phosphohydrolase type 1 (LPP1) which hydrolyze LPA into monoacylglycerol (MAG) in the outer leaflet of the cell membrane [26, 27] and LPA-acyltransferase (LPAAT), which transfer an acyl chain to LPA converting it into PA in the inner leaflet of the cell membrane [10]. Recently, a negative feedback loop has been described for the ATX-LPA axis [28]; in this mechanism, LPA signaling through its receptor $LPA_1/_3$ induces downregulation of ATX mRNA. Similarly, low levels of circulating LPA increase ATX mRNA, particularly in the adipose tissue of female Balb/c mice [28].

3. LPA Receptors

As previously mentioned, LPA signals through at least six G protein-coupled receptors LPA_{1-6} (Figure 1(b)): gene names are *LPAR1-LPAR6* (human) and *Lpar1-Lpar6* (mouse) [30, 31]. All LPA receptors are rhodopsin-like, with seven transmembrane domain receptors that range from 39 to 42 kDa and differ in their tissue distribution and downstream effectors [7]. According to their homology, there 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 18:2 is the most abundant species, the EDG family is more potently stimulated by acyl-LPA ($LPA_{1/2}$), and LPA_3 preferentially bounds to 2-acyl-LPA. The non-EGD family member LPA_5 is more potently stimulated by alkyl-LPA and LPA_6 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_1 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 $G\alpha_i$. Also known as EDG-2, Vgz-1 was later renamed LPA_1. Right after its discovery, two other orphan receptors, LPA_2 and LPA_3, were identified based on their homology to LPA_1 [36–38].

LPA_1 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, $G\alpha_{i/0}$, $G\alpha_{q/11}$, and $G\alpha_{12/13}$, 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^{2+} 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_1 is found in the ventricular zone, superficial marginal zone, and meninges. After birth, LPA_1 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*$^{-/-}$ 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_1 has been closely related to the induction of neuropathic pain due to nerve injury via LPA_1/RhoA/rock-mediated demyelination with a subsequent loss of the structural and functional integrity of neurons, as discussed elsewhere [42].

LPA_2 receptor (EDG-4) has a ~50–60% homology to LPA_1, 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_2 couples to the same G proteins as LPA_1 (Figure 1(b)): $G\alpha_{i/0}$, $G\alpha_{q/11}$, and $G\alpha_{12/13}$ [36, 39]; therefore, it can similarly activate downstream signaling but, unlike LPA_1, can also promote migration through the focal adhesion molecule TRIP6 [43, 44]. LPA_2 activation is associated with survival and migration. Compared with LPA_1, 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_2 knockout mice are mostly normal, suggesting a possible functional redundancy in relation to LPA_1. A *Lpar1*$^{-/-}$ *and Lpar2*$^{-/-}$ model has also been evaluated [46]. In this model, *Lpar1*$^{-/-}$ phenotype predominated with 50% perinatal lethality, cranial malformations, and reduced body size, but it also exhibited frontal hematomas [46].

LPA_3 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_1 and LPA_2, respectively, and is located on Chr1p22.3-p31.1 [30, 38, 39]. LPA_3 couples to G proteins, $G\alpha_{i/0}$ and $G\alpha_{11/q}$ (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 potently activated by 2-acyl-LPA with unsaturated fatty acids [2]. In humans, LPA_3 is expressed in heart, lung, pancreas, prostate, testis, ovaries, and brain [37]. In mice, it is expressed in testis, kidney, lung,

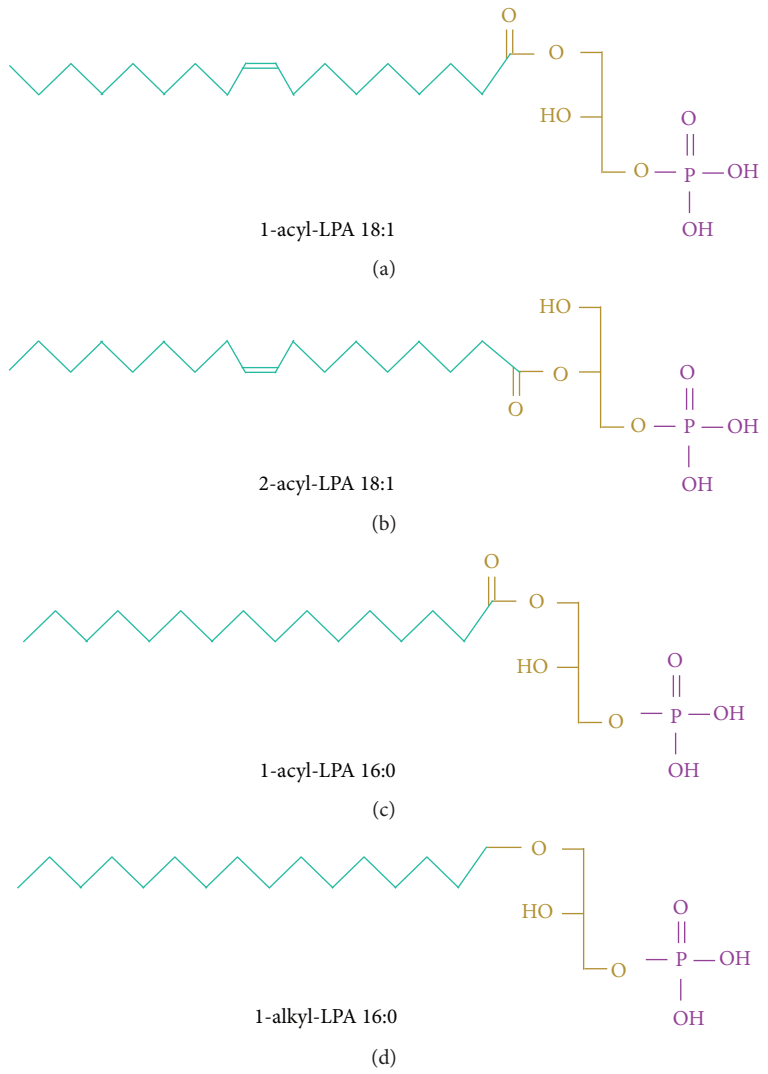

Figure 2: LPA species. LPA is derived from phospholipids with different lengths and saturations. (a) 18 carbon LPA species with an acyl group in sn-1 position and one saturation are the most potent activator of the LPA_1 and LPA_2 receptors [7]. (b) Acyl LPA with 18 carbons, one saturation, and the fatty acid chain in sn-2 position are the most potent activator of LPA_3 and LPA_6 [2, 34]. (c) An alkyl-LPA species with 16 carbons and no saturation are the most potent activator of LPA_5 receptor [33].

intestine, and moderately, small intestine [39]. Functional deletion of LPA_3 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 LPA_{1-3} male mice, an independent of testosterone signaling reduced sperm count and mating activity was found [49]. This evidence suggests the role of LPA_3 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 LPA_{1-3}, but it specifically binds to LPA. Its signaling promotes an increase in intracellular Ca^{2+} concentration and adenylyl cyclase activity in "LPA receptor-null" cells exogenously expressing P2Y9 [50]. Soon, LPA_5 and LPA_6 description followed [51–55].

LPA_4 (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: $G\alpha_{i/0}$, $G\alpha_{11/q}$, $G\alpha_{12/13,}$ and $G\alpha_s$ (Figure 1(b)) [57]. LPA_4 signaling promotes Rho-mediated neurite retraction and stresses fiber formation, Ca^{2+} mobilization, and regulation of cAMP concentration [57]. In humans, LPA_4 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].

LPA_5 (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 LPA_4 [51, 52]. LPA_5 couples

to G proteins, $G\alpha_{11/q}$ and $G\alpha_{12/13}$ (Figure 1(b)), by which Ca^{2+} mobilization, inositol phosphate production, neurite retraction, and stress fiber formation are mediated [51, 52]. It has been reported that LPA_5 preferentially binds to alkyl-LPA (16:0), rather than acyl-LPA (18:1) [33]. LPA_5 is found in heart, placenta, spleen, brain, lung, and gut in humans [51]. It is also highly expressed in the lymphocyte compartment of the gastrointestinal tract and platelets [51, 60]. In mice, it is found in the brain, heart, kidney, liver, lung, muscle, skin, spleen, stomach, small intestine, testis, and thymus [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 LPA_1 [62].

LPA_6 (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 LPA_4 [50], it is the closest receptor and is located on Chr13q14 [30, 55]. LPA_6 couples to $G\alpha_{i/0}$ and $G\alpha_{12/13}$ (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 LPA_6 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 demonstrate 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, LPA_4 expression in colon cancer cells (DLD1 and HTC116) suppresses cell migration and invasion compared to null-LPA_4 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 mice melanoma cells, LPA_5 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, LPA_6 expression significantly reduced cell growth and motility [63].

In rat lung adenocarcinoma, loss of LPA_3 due to methylation of the promoter enhances tumor progression by increasing invasion, suggesting a protective role of LPA_3 in this neoplasia [66]. By contrast, in human fibrosarcoma, LPA_4 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, LPA_5 is highly expressed due to unmethylation of the promoter, and cells expressing only LPA_5 showed enhanced proliferation, migration, and invasion [68]. Moreover, hepatocellular carcinoma (HCC) cells overexpressing LPA_6 sustain an increase in tumor growth, migration, and invasion. Moreover, LPA_6 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 δ (PKCδ) 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-adjacent B lymphocytes [92] and that LPA_5 may play a key role in the progression of these carcinomas [68], while LPA_3 could have a protective role [66]. Furthermore, LPA and other phospholipid levels are upregulated as a side effect of chemo- 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 LPA_{1-3} 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 LPA_2, 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 twofold reduction in at least 20 of these inflammatory mediators in the tumor-adjacent mammary adipose tissue-reducing inflammation and tumorigenesis [95]. Additionally, expression of LPA_{1-3} increased phosphorylation of STAT3, STAT5, NFκB and ATF2, 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 LPA_{1-2}. 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 LPA_{1-3} receptors showed more invasiveness compared to knockdowns. Moreover, via LPA_{2-3}, 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, LPA_6 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 IC_{50} = 101 nM *in vivo*	Preclinical	(i) Inflammation (ii) Glioblastoma	[133–135]
ONO-8430506	ATX	Direct binding to ATX. Inhibits lysoPLD activity. IC_{50} = 4.5 nM isolated ATX IC_{50} = 4.1–11.6 nM *in vivo*	Preclinical	(i) Breast cancer (ii) BCa metastasis (iii) Thyroid cancer	[19, 28, 121, 136]
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 LPA_2 LPA_3 LPA_4 LPA_5	Direct binding to ATX. Inhibits lysoPLD activity. IC_{50}: 600 nM ex vivo Direct binding and inhibition of LPA_{1-5}	Preclinical	(i) Rheumatoid arthritis (ii) Breast cancer (iii) Pancreatic cancer (iv) Glioma	[142–145]

etiologies 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 CD8 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 in xenograft models [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],

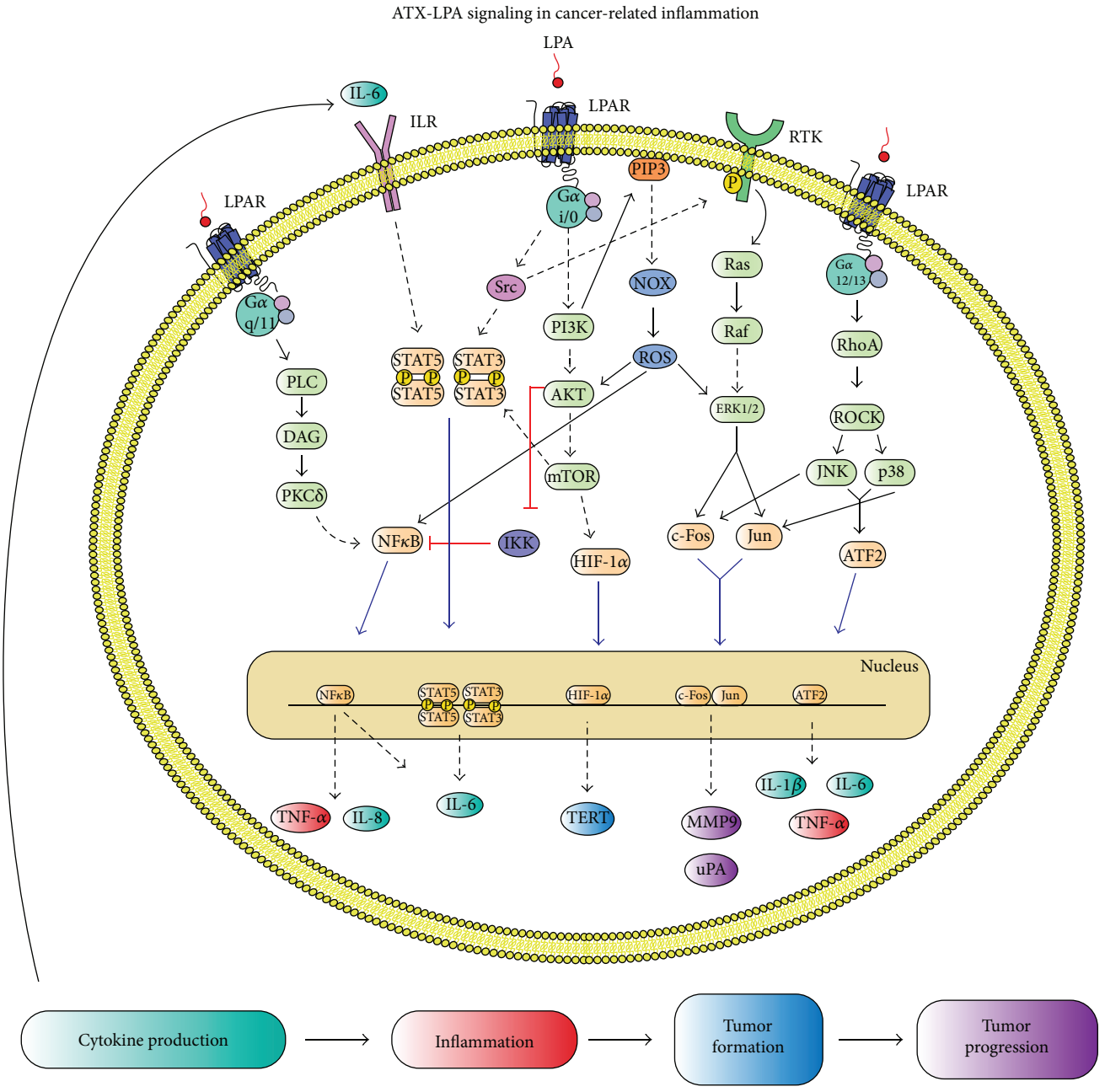

Figure 3: ATX-LPA axis promotes cancer-related inflammation. In CRI, LPA acts on its receptors via $G\alpha_{q/11}$, $G\alpha_{i/0}$, and $G\alpha_{12/13}$. $G\alpha_{q/11}$ induces NFκB activation through PKCδ promoting TNF-α, IL-8, and IL-6 production. $G\alpha_{i/0}$ induces the PI3K/AKT/mTOR pathway culminating in NFκB and HIF-1α translocation to the nucleus. HIF-1α induces the transcription of TERT enabling replicative immortality. $G\alpha_{i/0}$ can also transactivate Src kinase and crosstalk with EGFR, to induce extracellular matrix degrading proteins, and STAT-3 signaling pathway to further induce cytokine production. PI3K signaling promotes ROS production and activation of AKT, ERK1/2, and NFκB. On the other hand, $G\alpha_{12/13}$/RhoA/ROCK signaling causes activation of transcription factor ATF2 to induce further proinflammatory mediator production. Finally, cytokine production, particularly IL-6, can interact with their IL receptors and promote STAT5 and STAT3 activation. In all, these pathways maintain a proinflammatory environment that leads to malignant transformation. Dashed lines denote that other proteins participate in the pathways and were omitted to summarize information. This figure is reproduced from Liu et al. [124] (under the Creative Commons Attribution License/public domain).

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

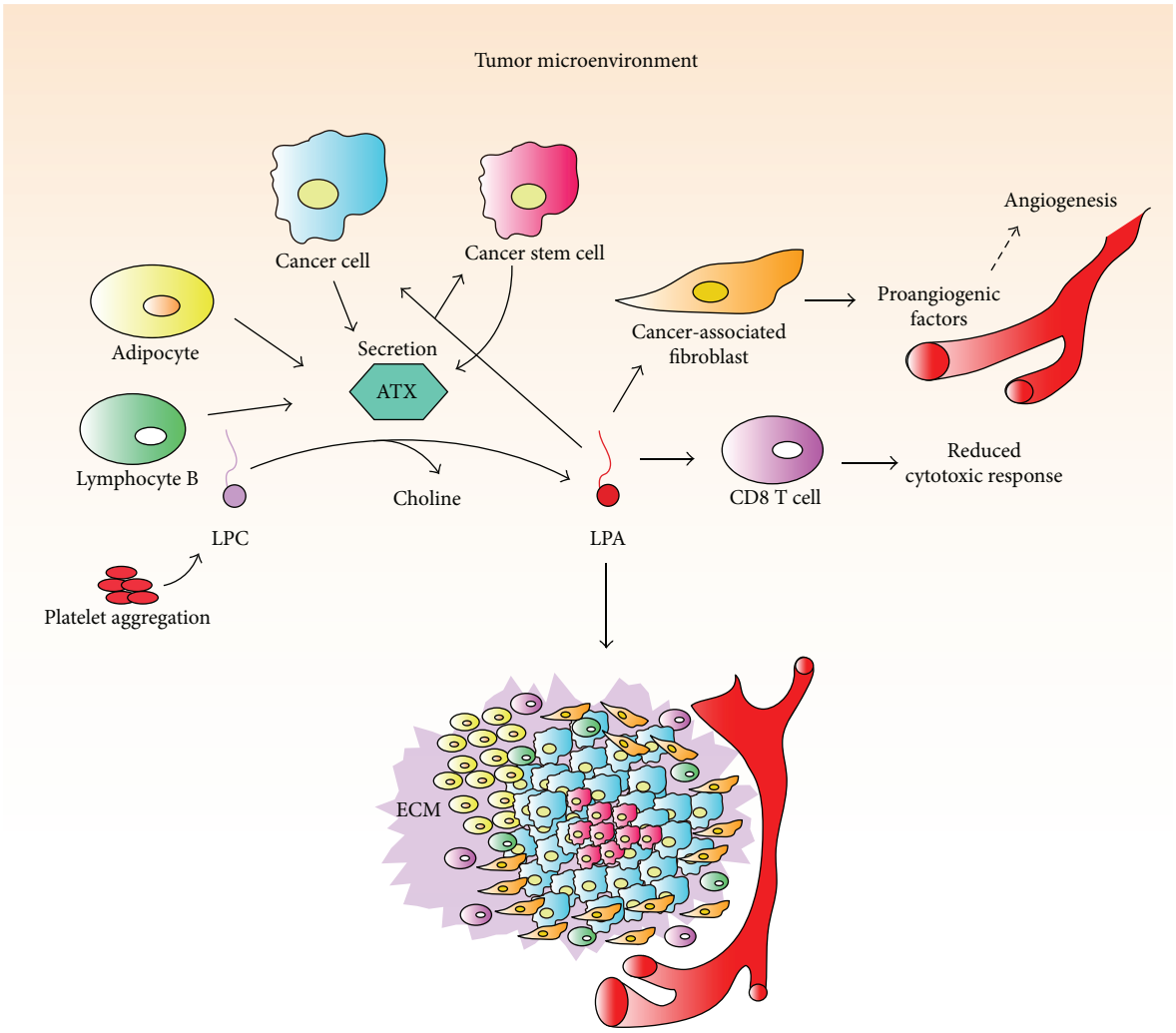

Figure 4: ATX-LPA signaling in tumor microenvironment. ATX hydrolyzes LPC to produce LPA from circulating LPC and platelet-derived LPC. ATX is mainly released into the tumor microenvironment by tumor-adjacent adipocytes and B lymphocytes but cancer cells and cancer stem cells also secrete this enzyme. LPA signals through its receptors to induce proliferation and invasion in cancer cells and cancer stem cells. LPA signaling induces angiogenesis through the recruitment of CAFS; it also reduces cytotoxic immune response via CD8 T cells. ECM (extracellular matrix).

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 mediate cancer-related inflammation through diverse signaling pathways, crosstalk, and positive loops. Therefore, it enhances a proinflammatory microenvironment and, at the same time, ATX-LPA signaling augments. Breaking the inflammatory cycle and blocking LPA signaling and production should provide an innovative treatment for cancer by decreasing CRI, tumor growth, metastasis, and resistance to cancer treatments. Recent evidence in cirrhosis patients point to this axis as a key regulator in HCC tumorigenesis, 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: Phosphatidylserine
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: Adenylyl 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
HBEpCs: 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
NFκB: 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: Krüpple-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.

Acknowledgments

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References

[1] W. H. Moolenaar, "Development of our current understanding of bioactive lysophospholipids," *Annals of the New York Academy of Sciences*, vol. 905, pp. 1–10, 2000.

[2] K. Bandoh, J. Aoki, A. Taira, M. Tsujimoto, H. Arai, and K. Inoue, "Lysophosphatidic acid (LPA) receptors of the EDG family are differentially activated by LPA species," *FEBS Letters*, vol. 478, no. 1-2, pp. 159–165, 2000.

[3] W. H. Moolenaar, L. A. van Meeteren, and B. N. G. Giepmans, "The ins and outs of lysophosphatidic acid signaling," *BioEssays*, vol. 26, no. 8, pp. 870–881, 2004.

[4] I. Gonzalez-Gil, D. Zian, H. Vazquez-Villa, S. Ortega-Gutierrez, and M. L. Lopez-Rodriguez, "The status of the lysophosphatidic acid receptor type 1 (LPA_1R)," *MedChemComm*, vol. 6, no. 1, pp. 13–23, 2015.

[5] G. B. Mills and W. H. Moolenaar, "The emerging role of lysophosphatidic acid in cancer," *Nature Reviews Cancer*, vol. 3, no. 8, pp. 582–591, 2003.

[6] J. W. Choi and J. Chun, "Lysophospholipids and their receptors in the central nervous system," *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids*, vol. 1831, no. 1, pp. 20–32, 2013.

[7] Y. C. Yung, N. C. Stoddard, and J. Chun, "LPA receptor signaling: pharmacology, physiology, and pathophysiology," *Journal of Lipid Research*, vol. 55, no. 7, pp. 1192–1214, 2014.

[8] J. Mazereeuw-Hautier, S. Gres, M. Fanguin et al., "Production of lysophosphatidic acid in blister fluid: involvement of a lysophospholipase D activity," *Journal of Investigative Dermatology*, vol. 125, no. 3, pp. 421–427, 2005.

[9] L. A. van Meeteren and W. H. Moolenaar, "Regulation and biological activities of the autotaxin–LPA axis," *Progress in Lipid Research*, vol. 46, no. 2, pp. 145–160, 2007.

[10] C. Pagès, M.-F. Simon, P. Valet, and J. S. Saulnier-Blache, "Lysophosphatidic acid synthesis and release," *Prostaglandins & Other Lipid Mediators*, vol. 64, no. 1–4, pp. 1–10, 2001.

[11] T. Sano, D. Baker, T. Virag et al., "Multiple mechanisms linked to platelet activation result in lysophosphatidic acid and sphingosine 1-phosphate generation in blood," *Journal of Biological Chemistry*, vol. 277, no. 24, pp. 21197–21206, 2002.

[12] D. L. Baker, D. M. Desiderio, D. D. Miller, B. Tolley, and G. J. Tigyi, "Direct quantitative analysis of lysophosphatidic acid molecular species by stable isotope dilution electrospray ionization liquid chromatography–mass spectrometry," *Analytical Biochemistry*, vol. 292, no. 2, pp. 287–295, 2001.

[13] J. W. Choi, D. R. Herr, K. Noguchi et al., "LPA receptors: subtypes and biological actions," *Annual Review of Pharmacology and Toxicology*, vol. 50, no. 1, pp. 157–186, 2010.

[14] J. Aoki, A. Inoue, and S. Okudaira, "Two pathways for lysophosphatidic acid production," *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids*, vol. 1781, no. 9, pp. 513–518, 2008.

[15] A. Perrakis and W. H. Moolenaar, "Autotaxin: structure-function and signaling," *Journal of Lipid Research*, vol. 55, no. 6, pp. 1010–1018, 2014.

[16] H. Kawagoe, O. Soma, J. Goji et al., "Molecular cloning and chromosomal assignment of the human brain-type phosphodiesterase I/nucleotide pyrophosphatase gene (*PDNP2*)," *Genomics*, vol. 30, no. 2, pp. 380–384, 1995.

[17] A. Tokumura, E. Majima, Y. Kariya et al., "Identification of human plasma lysophospholipase D, a lysophosphatidic acid-producing enzyme, as autotaxin, a multifunctional phosphodiesterase," *Journal of Biological Chemistry*, vol. 277, no. 42, pp. 39436–39442, 2002.

[18] M. Umezu-Goto, Y. Kishi, A. Taira et al., "Autotaxin has lysophospholipase D activity leading to tumor cell growth and motility by lysophosphatidic acid production," *The Journal of Cell Biology*, vol. 158, no. 2, pp. 227–233, 2002.

[19] M. G. K. Benesch, X. Tang, T. Maeda et al., "Inhibition of autotaxin delays breast tumor growth and lung metastasis in mice," *The FASEB Journal*, vol. 28, no. 6, pp. 2655–2666, 2014.

[20] L. A. Van Meeteren, P. Ruurs, C. Stortelers et al., "Autotaxin, a secreted lysophospholipase D, is essential for blood vessel formation during development," *Molecular and Cellular Biology*, vol. 26, no. 13, pp. 5015–5022, 2006.

[21] M. Tanaka, S. Okudaira, Y. Kishi et al., "Autotaxin stabilizes blood vessels and is required for embryonic vasculature by producing lysophosphatidic acid," *Journal of Biological Chemistry*, vol. 281, no. 35, pp. 25822–25830, 2006.

[22] R. Dusaulcy, C. Rancoule, S. Grès et al., "Adipose-specific disruption of autotaxin enhances nutritional fattening and reduces plasma lysophosphatidic acid," *Journal of Lipid Research*, vol. 52, no. 6, pp. 1247–1255, 2011.

[23] M. G. K. Benesch, Y. M. Ko, T. P. W. McMullen, and D. N. Brindley, "Autotaxin in the crosshairs: taking aim at cancer and other inflammatory conditions," *FEBS Letters*, vol. 588, no. 16, pp. 2712–2727, 2014.

[24] G. Ferry, E. Tellier, A. Try et al., "Autotaxin is released from adipocytes, catalyzes lysophosphatidic acid synthesis, and activates preadipocyte proliferation. Up-regulated expression with adipocyte differentiation and obesity," *Journal of Biological Chemistry*, vol. 278, no. 20, pp. 18162–18169, 2003.

[25] H. M. H. G. Albers, A. Dong, L. A. van Meeteren et al., "Boronic acid-based inhibitor of autotaxin reveals rapid turnover of LPA in the circulation," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 107, no. 16, pp. 7257–7262, 2010.

[26] J. L. Tomsig, A. H. Snyder, E. V. Berdyshev et al., "Lipid phosphate phosphohydrolase type 1 (LPP1) degrades extracellular lysophosphatidic acid in vivo," *Biochemical Journal*, vol. 419, no. 3, pp. 611–618, 2009.

[27] X. Tang, M. G. K. Benesch, and D. N. Brindley, "Lipid phosphate phosphatases and their roles in mammalian physiology and pathology," *Journal of Lipid Research*, vol. 56, no. 11, pp. 2048–2060, 2015.

[28] M. G. K. Benesch, Y. Y. Zhao, J. M. Curtis, T. P. W. McMullen, and D. N. Brindley, "Regulation of autotaxin expression and secretion by lysophosphatidate and sphingosine 1-phosphate," *Journal of Lipid Research*, vol. 56, no. 6, pp. 1134–1144, 2015.

[29] V. A. Blaho and T. Hla, "Regulation of mammalian physiology, development, and disease by the sphingosine 1-phosphate and lysophosphatidic acid receptors," *Chemical Reviews*, vol. 111, no. 10, pp. 6299–6320, 2011.

[30] Y. Kihara, M. Maceyka, S. Spiegel, and J. Chun, "Lysophospholipid receptor nomenclature review: IUPHAR review 8," *British Journal of Pharmacology*, vol. 171, no. 15, pp. 3575–3594, 2014.

[31] J. Chun, T. Hla, K. R. Lynch, S. Spiegel, and W. H. Moolenaar, "International union of basic and clinical pharmacology. LXXVIII. Lysophospholipid receptor nomenclature," *Pharmacological Reviews*, vol. 62, no. 4, pp. 579–587, 2010.

[32] Y. Takuwa, N. Takuwa, and N. Sugimoto, "The Edg family G protein-coupled receptors for lysophospholipids: their signaling properties and biological activities," *The Journal of Biochemistry*, vol. 131, no. 6, pp. 767–771, 2002.

[33] K. Yanagida, Y. Kurikawa, T. Shimizu, and S. Ishii, "Current progress in non-Edg family LPA receptor research," *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids*, vol. 1831, no. 1, pp. 33–41, 2013.

[34] J. R. Williams, A. L. Khandoga, P. Goyal et al., "Unique ligand selectivity of the GPR92/LPA_5 lysophosphatidate receptor indicates role in human platelet activation," *Journal of Biological Chemistry*, vol. 284, no. 25, pp. 17304–17319, 2009.

[35] J. H. Hecht, J. A. Weiner, S. R. Post, and J. Chun, "Ventricular zone gene-1 (vzg-1) encodes a lysophosphatidic acid receptor expressed in neurogenic regions of the developing cerebral cortex," *The Journal of Cell Biology*, vol. 135, no. 4, pp. 1071–1083, 1996.

[36] S. An, T. Bleu, O. G. Hallmark, and E. J. Goetzl, "Characterization of a novel subtype of human G protein-coupled

receptor for lysophosphatidic acid," *Journal of Biological Chemistry*, vol. 273, no. 14, pp. 7906–7910, 1998.

[37] K. Bandoh, J. Aoki, H. Hosono et al., "Molecular cloning and characterization of a novel human G-protein-coupled receptor, EDG7, for lysophosphatidic acid," *Journal of Biological Chemistry*, vol. 274, no. 39, pp. 27776–27785, 1999.

[38] D. S. Im, C. E. Heise, M. A. Harding et al., "Molecular cloning and characterization of a lysophosphatidic acid receptor, Edg-7, expressed in prostate," *Molecular Pharmacology*, vol. 57, no. 4, pp. 753–759, 2000.

[39] J. J. Contos, I. Ishii, and J. Chun, "Lysophosphatidic acid receptors," *Molecular Pharmacology*, vol. 58, no. 6, pp. 1188–1196, 2000.

[40] Y. C. Yung, N. C. Stoddard, H. Mirendil, and J. Chun, "Lysophosphatidic acid signaling in the nervous system," *Neuron*, vol. 85, no. 4, pp. 669–682, 2015.

[41] J. J. A. Contos, N. Fukushima, J. A. Weiner, D. Kaushal, and J. Chun, "Requirement for the lp_{A1} lysophosphatidic acid receptor gene in normal suckling behavior," *Proceedings of the National Academy of Sciences*, vol. 97, no. 24, pp. 13384–13389, 2000.

[42] H. Ueda, H. Matsunaga, O. I. Olaposi, and J. Nagai, "Lysophosphatidic acid: chemical signature of neuropathic pain," *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids*, vol. 1831, no. 1, pp. 61–73, 2013.

[43] Y.-J. Lai, C.-S. Chen, W.-C. Lin, and F.-T. Lin, "C-Src-mediated phosphorylation of TRIP6 regulates its function in lysophosphatidic acid-induced cell migration," *Molecular and Cellular Biology*, vol. 25, no. 14, pp. 5859–5868, 2005.

[44] Y.-J. Lai, W.-C. Lin, and F.-T. Lin, "PTPL1/FAP-1 negatively regulates TRIP6 function in lysophosphatidic acid-induced cell migration," *Journal of Biological Chemistry*, vol. 282, no. 33, pp. 24381–24387, 2007.

[45] H. Ohuchi, A. Hamada, H. Matsuda et al., "Expression patterns of the lysophospholipid receptor genes during mouse early development," *Developmental Dynamics*, vol. 237, no. 11, pp. 3280–3294, 2008.

[46] J. J. A. Contos, I. Ishii, N. Fukushima et al., "Characterization of lpa_2 (*Edg4*) and lpa_1/lpa_2 (*Edg2*/*Edg4*) lysophosphatidic acid receptor knockout mice: signaling deficits without obvious phenotypic abnormality attributable to lpa_2," *Molecular and Cellular Biology*, vol. 22, no. 19, pp. 6921–6929, 2002.

[47] I. Ishii, J. J. Contos, N. Fukushima, and J. Chun, "Functional comparisons of the lysophosphatidic acid receptors, LP_{A1}/VZG-1/EDG-2, LP_{A2}/EDG-4, and LP_{A3}/EDG-7 in neuronal cell lines using a retrovirus expression system," *Molecular Pharmacology*, vol. 58, no. 5, pp. 895–902, 2000.

[48] X. Ye, K. Hama, J. J. A. Contos et al., "LPA_3-mediated lysophosphatidic acid signalling in embryo implantation and spacing," *Nature*, vol. 435, no. 7038, pp. 104–108, 2005.

[49] X. Ye, M. K. Skinner, G. Kennedy, and J. Chun, "Age-dependent loss of sperm production in mice via impaired lysophosphatidic acid signaling," *Biology of Reproduction*, vol. 79, no. 2, pp. 328–336, 2008.

[50] K. Noguchi, S. Ishii, and T. Shimizu, "Identification of $p2y_9$/GPR23 as a novel G protein-coupled receptor for lysophosphatidic acid, structurally distant from the Edg family," *Journal of Biological Chemistry*, vol. 278, no. 28, pp. 25600–25606, 2003.

[51] K. Kotarsky, Å. Boketoft, J. Bristulf et al., "Lysophosphatidic acid binds to and activates GPR92, a G protein-coupled receptor highly expressed in gastrointestinal lymphocytes," *Journal of Pharmacology and Experimental Therapeutics*, vol. 318, no. 2, pp. 619–628, 2006.

[52] C.-W. Lee, R. Rivera, S. Gardell, A. E. Dubin, and J. Chun, "GPR92 as a new G12/13- and G_q-coupled lysophosphatidic acid receptor that increases cAMP, LPA_5," *Journal of Biological Chemistry*, vol. 281, no. 33, pp. 23589–23597, 2006.

[53] K. Yanagida, K. Masago, H. Nakanishi et al., "Identification and characterization of a novel lysophosphatidic acid receptor, p2y5/LPA_6," *Journal of Biological Chemistry*, vol. 284, no. 26, pp. 17731–17741, 2009.

[54] M. Lee, S. Choi, G. Halldén, S. J. Yo, D. Schichnes, and G. W. Aponte, "P2Y5 is a $G\alpha_i$, $G\alpha_{12/13}$ G protein-coupled receptor activated by lysophosphatidic acid that reduces intestinal cell adhesion," *American Journal of Physiology - Gastrointestinal and Liver Physiology*, vol. 297, no. 4, pp. G641–G654, 2009.

[55] S. M. Pasternack, I. von Kügelgen, K. Al Aboud et al., "G protein–coupled receptor P2Y5 and its ligand LPA are involved in maintenance of human hair growth," *Nature Genetics*, vol. 40, no. 3, pp. 329–334, 2008.

[56] R. Janssens, J. M. Boeynaems, M. Godart, and D. Communi, "Cloning of a human heptahelical receptor closely related to the $P2Y_5$receptor," *Biochemical and Biophysical Research Communications*, vol. 236, no. 1, pp. 106–112, 1997.

[57] C.-W. Lee, R. Rivera, A. E. Dubin, and J. Chun, "LPA_4/GPR23 is a lysophosphatidic acid (LPA) receptor utilizing G_s-, G_q/G_i-mediated calcium signaling and G12/13-mediated rho activation," *Journal of Biological Chemistry*, vol. 282, no. 7, pp. 4310–4317, 2007.

[58] Z. Lee, C.-T. Cheng, H. Zhang et al., "Role of LPA_4/p2y9/GPR23 in negative regulation of cell motility," *Molecular Biology of the Cell*, vol. 19, no. 12, pp. 5435–5445, 2008.

[59] H. Sumida, K. Noguchi, Y. Kihara et al., "LPA_4 regulates blood and lymphatic vessel formation during mouse embryogenesis," *Blood*, vol. 116, no. 23, pp. 5060–5070, 2010.

[60] S. Amisten, O. O. Braun, A. Bengtsson, and D. Erlinge, "Gene expression profiling for the identification of G-protein coupled receptors in human platelets," *Thrombosis Research*, vol. 122, no. 1, pp. 47–57, 2008.

[61] Z. Callaerts-Vegh, S. Leo, B. Vermaercke, T. Meert, and R. D'Hooge, "LPA5 receptor plays a role in pain sensitivity, emotional exploration and reversal learning," *Genes, Brain and Behavior*, vol. 11, pp. 1009–1019, 2012.

[62] M.-E. Lin, R. R. Rivera, and J. Chun, "Targeted deletion of LPA_5 identifies novel roles for lysophosphatidic acid signaling in development of neuropathic pain," *The Journal of Biological Chemistry*, vol. 287, no. 21, pp. 17608–17617, 2012.

[63] K. Takahashi, K. Fukushima, Y. Onishi et al., "Lysophosphatidic acid (LPA) signaling via LPA_4 and LPA_6 negatively regulates cell motile activities of colon cancer cells," *Biochemical and Biophysical Research Communications*, vol. 483, no. 1, pp. 652–657, 2017.

[64] M. Araki, M. Kitayoshi, Y. Dong et al., "Inhibitory effects of lysophosphatidic acid receptor-5 on cellular functions of sarcoma cells," *Growth Factors*, vol. 32, no. 3-4, pp. 117–122, 2014.

[65] M. Jongsma, E. Matas-Rico, A. Rzadkowski, K. Jalink, and W. H. Moolenaar, "LPA is a chemorepellent for B16 melanoma cells: action through the cAMP-elevating LPA_5 receptor," *PLoS One*, vol. 6, no. 12, article e29260, 2011.

[66] M. Hayashi, K. Okabe, Y. Yamawaki et al., "Loss of lysophosphatidic acid receptor-3 enhances cell migration in rat lung tumor cells," *Biochemical and Biophysical Research Communications*, vol. 405, no. 3, pp. 450–454, 2011.

[67] K. Harper, D. Arsenault, S. Boulay-Jean, A. Lauzier, F. Lucien, and C. M. Dubois, "Autotaxin promotes cancer invasion via the lysophosphatidic acid receptor 4: participation of the cyclic AMP/EPAC/Rac1 signaling pathway in invadopodia formation," *Cancer Research*, vol. 70, no. 11, pp. 4634–4643, 2010.

[68] K. Okabe, M. Hayashi, Y. Yamawaki et al., "Possible involvement of lysophosphatidic acid receptor-5 gene in the acquisition of growth advantage of rat tumor cells," *Molecular Carcinogenesis*, vol. 50, no. 8, pp. 635–642, 2011.

[69] A. Mazzocca, F. Dituri, F. De Santis et al., "Lysophosphatidic acid receptor LPAR6 supports the tumorigenicity of hepatocellular carcinoma," *Cancer Research*, vol. 75, no. 3, pp. 532–543, 2015.

[70] F. Balkwill and A. Mantovani, "Inflammation and cancer: back to Virchow?," *The Lancet*, vol. 357, no. 9255, pp. 539–545, 2001.

[71] F. Colotta, P. Allavena, A. Sica, C. Garlanda, and A. Mantovani, "Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability," *Carcinogenesis*, vol. 30, no. 7, pp. 1073–1081, 2009.

[72] S. Deivendran, K. H. Marzook, and M. Radhakrishna Pillai, "The role of inflammation in cervical cancer," *Advances in Experimental Medicine and Biology*, vol. 816, pp. 377–399, 2014.

[73] J. G. Fox and T. C. Wang, "Inflammation, atrophy, and gastric cancer," *The Journal of Clinical Investigation*, vol. 117, no. 1, pp. 60–69, 2007.

[74] H. Barash, E. R. Gross, Y. Edrei et al., "Accelerated carcinogenesis following liver regeneration is associated with chronic inflammation-induced double-strand DNA breaks," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 107, no. 5, pp. 2207–2212, 2010.

[75] D. G. DeNardo and L. M. Coussens, "Inflammation and breast cancer. Balancing immune response: crosstalk between adaptive and innate immune cells during breast cancer progression," *Breast Cancer Research*, vol. 9, no. 4, p. 212, 2007.

[76] A. M. Al Murri, J. M. S. Bartlett, P. A. Canney, J. C. Doughty, C. Wilson, and D. C. McMillan, "Evaluation of an inflammation-based prognostic score (GPS) in patients with metastatic breast cancer," *British Journal of Cancer*, vol. 94, no. 2, pp. 227–230, 2006.

[77] N. Azad, Y. Rojanasakul, and V. Vallyathan, "Inflammation and lung cancer: roles of reactive oxygen/nitrogen species," *Journal of Toxicology and Environmental Health Part B: Critical Reviews*, vol. 11, no. 1, pp. 1–15, 2008.

[78] K. S. Sfanos and A. M. De Marzo, "Prostate cancer and inflammation: the evidence," *Histopathology*, vol. 60, no. 1, pp. 199–215, 2012.

[79] A. Macciò and C. Madeddu, "Inflammation and ovarian cancer," *Cytokine*, vol. 58, no. 2, pp. 133–147, 2012.

[80] V. Guarino, M. D. Castellone, E. Avilla, and R. M. Melillo, "Thyroid cancer and inflammation," *Molecular and Cellular Endocrinology*, vol. 321, no. 1, pp. 94–102, 2010.

[81] J. Liang, M. Nagahashi, E. Y. Kim et al., "Sphingosine-1-phosphate links persistent STAT3 activation, chronic intestinal inflammation, and development of colitis-associated cancer," *Cancer Cell*, vol. 23, no. 1, pp. 107–120, 2013.

[82] E. R. Rayburn, S. J. Ezell, and R. Zhang, "Anti-inflammatory agents for cancer therapy," *Molecular and Cellular Pharmacology*, vol. 1, no. 1, pp. 29–43, 2009.

[83] C. M. Ulrich, J. Bigler, and J. D. Potter, "Non-steroidal anti-inflammatory drugs for cancer prevention: promise, perils and pharmacogenetics," *Nature Reviews Cancer*, vol. 6, no. 2, pp. 130–140, 2006.

[84] D. Hanahan and R. A. Weinberg, "Hallmarks of cancer: the next generation," *Cell*, vol. 144, no. 5, pp. 646–674, 2011.

[85] Z. Bai, L. Cai, E. Umemoto et al., "Constitutive lymphocyte transmigration across the basal lamina of high endothelial venules is regulated by the Autotaxin/lysophosphatidic acid Axis," *The Journal of Immunology*, vol. 190, no. 5, pp. 2036–2048, 2013.

[86] S. Knowlden and S. N. Georas, "The autotaxin-LPA axis emerges as a novel regulator of lymphocyte homing and inflammation," *The Journal of Immunology*, vol. 192, no. 3, pp. 851–857, 2014.

[87] D. N. Brindley, M. G. K. Benesch, and M. M. Murph, "Autotaxin–an enzymatic augmenter of malignant progression linked to inflammation," in *Melanoma - Current Clinical Management and Future Therapeutics*, M. Murph, Ed., p. 12, InTech, Rijeka, 2015.

[88] R. Cummings, Y. Zhao, D. Jacoby et al., "Protein kinase Cδ mediates lysophosphatidic acid-induced NF-κB activation and interleukin-8 secretion in human bronchial epithelial cells," *The Journal of Biological Chemistry*, vol. 279, no. 39, pp. 41085–41094, 2004.

[89] Y. Zhao, D. He, B. Saatian et al., "Regulation of lysophosphatidic acid-induced epidermal growth factor receptor transactivation and interleukin-8 secretion in human bronchial epithelial cells by protein kinase Cδ, Lyn kinase, and matrix metalloproteinases," *The Journal of Biological Chemistry*, vol. 281, no. 28, pp. 19501–19511, 2006.

[90] Y. Li, H. Du, Y. Qin, J. Roberts, O. W. Cummings, and C. Yan, "Activation of the signal transducers and activators of the transcription 3 pathway in alveolar epithelial cells induces inflammation and adenocarcinomas in mouse lung," *Cancer Research*, vol. 67, no. 18, pp. 8494–8503, 2007.

[91] X. Xu and G. D. Prestwich, "Inhibition of tumor growth and angiogenesis by a lysophosphatidic acid antagonist in an engineered three-dimensional lung cancer xenograft model," *Cancer*, vol. 116, no. 7, pp. 1739–1750, 2010.

[92] Y. Yang, L. Mou, N. Liu, and M. S. Tsao, "Autotaxin expression in non-small-cell lung cancer," *American Journal of Respiratory Cell and Molecular Biology*, vol. 21, no. 2, pp. 216–222, 1999.

[93] G. Schneider, Z. P. Sellers, K. Bujko, S. S. Kakar, M. Kucia, and M. Z. Ratajczak, "Novel pleiotropic effects of bioactive phospholipids in human lung cancer metastasis," *Oncotarget*, vol. 8, no. 35, pp. 58247–58263, 2017.

[94] S. Liu, M. Umezu-Goto, M. Murph et al., "Expression of autotaxin and lysophosphatidic acid receptors increases mammary tumorigenesis, invasion, and metastases," *Cancer Cell*, vol. 15, no. 6, pp. 539–550, 2009.

[95] M. G. K. Benesch, X. Tang, J. Dewald et al., "Tumor-induced inflammation in mammary adipose tissue stimulates a vicious cycle of autotaxin expression and breast cancer

progression," *The FASEB Journal*, vol. 29, no. 9, pp. 3990–4000, 2015.

[96] M. David, E. Wannecq, F. Descotes et al., "Cancer cell expression of autotaxin controls bone metastasis formation in mouse through lysophosphatidic acid-dependent activation of osteoclasts," *PLoS One*, vol. 5, no. 3, article e9741, 2010.

[97] H. Yu, D. Pardoll, and R. Jove, "STATs in cancer inflammation and immunity: a leading role for STAT3," *Nature Reviews Cancer*, vol. 9, no. 11, pp. 798–809, 2009.

[98] G. Meng, X. Tang, Z. Yang et al., "Implications for breast cancer treatment from increased autotaxin production in adipose tissue after radiotherapy," *The FASEB Journal*, vol. 31, no. 9, pp. 4064–4077, 2017.

[99] E. J. Seo, Y. W. Kwon, I. H. Jang et al., "Autotaxin regulates maintenance of ovarian cancer stem cells through lysophosphatidic acid-mediated autocrine mechanism," *Stem Cells*, vol. 34, no. 3, pp. 551–564, 2016.

[100] Y. Xu, Z. Shen, D. W. Wiper et al., "Lysophosphatidic acid as a potential biomarker for ovarian and other gynecologic cancers," *JAMA*, vol. 280, no. 8, pp. 719–723, 1998.

[101] Y.-Y. Li, W.-C. Zhang, J.-L. Zhang et al., "Plasma levels of lysophosphatidic acid in ovarian cancer versus controls: a meta-analysis," *Lipids in Health and Disease*, vol. 14, no. 1, p. 72, 2015.

[102] S.-Y. Zhang, W. Shi, P. Cheng, and M. J. Zaworotko, "A mixed-crystal lanthanide zeolite-like metal–organic framework as a fluorescent indicator for lysophosphatidic acid, a cancer biomarker," *Journal of the American Chemical Society*, vol. 137, no. 38, pp. 12203–12206, 2015.

[103] J. A. Saunders, L. C. Rogers, C. Klomsiri, L. B. Poole, and L. W. Daniel, "Reactive oxygen species mediate lysophosphatidic acid induced signaling in ovarian cancer cells," *Free Radical Biology & Medicine*, vol. 49, no. 12, pp. 2058–2067, 2010.

[104] K. Yang, D. Zheng, X. Deng, L. Bai, Y. Xu, and Y.-S. Cong, "Lysophosphatidic acid activates telomerase in ovarian cancer cells through hypoxia-inducible factor-1α and the PI3K pathway," *Journal of Cellular Biochemistry*, vol. 105, no. 5, pp. 1194–1201, 2008.

[105] S. Yu, M. M. Murph, Y. Lu et al., "Lysophosphatidic acid receptors determine tumorigenicity and aggressiveness of ovarian cancer cells," *Journal of the National Cancer Institute*, vol. 100, no. 22, pp. 1630–1642, 2008.

[106] V. C. Estrella, A. M. Eder, S. Liu et al., "Lysophosphatidic acid induction of urokinase plasminogen activator secretion requires activation of the p38MAPK pathway," *International Journal of Oncology*, vol. 31, no. 2, pp. 441–449, 2007.

[107] S. Nakagawa, L. Wei, W. M. Song et al., "Molecular liver cancer prevention in cirrhosis by organ transcriptome analysis and lysophosphatidic acid pathway inhibition," *Cancer Cell*, vol. 30, pp. 879–890, 2017.

[108] N. Watanabe, H. Ikeda, K. Nakamura et al., "Both plasma lysophosphatidic acid and serum autotaxin levels are increased in chronic hepatitis C," *Journal of Clinical Gastroenterology*, vol. 41, no. 6, pp. 616–623, 2007.

[109] J.-M. Wu, Y. Xu, N. J. Skill et al., "Autotaxin expression and its connection with the TNF-alpha-NF-κB axis in human hepatocellular carcinoma," *Molecular Cancer*, vol. 9, no. 1, p. 71, 2010.

[110] A. Mazzocca, F. Dituri, L. Lupo, M. Quaranta, S. Antonaci, and G. Giannelli, "Tumor-secreted lysophostatidic acid accelerates hepatocellular carcinoma progression by promoting differentiation of peritumoral fibroblasts in myofibroblasts," *Hepatology*, vol. 54, no. 3, pp. 920–930, 2011.

[111] D. J. Erstad, A. M. Tager, Y. Hoshida, and B. C. Fuchs, "The autotaxin-lysophosphatidic acid pathway emerges as a therapeutic target to prevent liver cancer," *Molecular & Cellular Oncology*, vol. 4, no. 3, article e1311827, 2017.

[112] D. Shida, T. Watanabe, J. Aoki et al., "Aberrant expression of lysophosphatidic acid (LPA) receptors in human colorectal cancer," *Laboratory Investigation*, vol. 84, no. 10, pp. 1352–1362, 2004.

[113] H. Sun, J. Ren, Q. Zhu, F.-Z. Kong, L. Wu, and B.-R. Pan, "Effects of lysophosphatidic acid on human colon cancer cells and its mechanisms of action," *World Journal of Gastroenterology*, vol. 15, no. 36, pp. 4547–4555, 2009.

[114] S. Lin, D. Wang, S. Iyer et al., "The absence of LPA_2 attenuates tumor formation in an experimental model of colitis-associated cancer," *Gastroenterology*, vol. 136, no. 5, pp. 1711–1720, 2009.

[115] S. Lin, S.-J. Lee, H. Shim, J. Chun, and C. C. Yun, "The absence of LPA receptor 2 reduces the tumorigenesis by APC^{Min} mutation in the intestine," *American Journal of Physiology - Gastrointestinal and Liver Physiology*, vol. 299, no. 5, pp. G1128–G1138, 2010.

[116] S. K. Oda, P. Strauch, Y. Fujiwara et al., "Lysophosphatidic acid inhibits CD8 T-cell activation and control of tumor progression," *Cancer Immunology Research*, vol. 1, no. 4, pp. 245–255, 2013.

[117] Y. Liao, G. Mu, L. Zhang, W. Zhou, J. Zhang, and H. Yu, "Lysophosphatidic acid stimulates activation of focal adhesion kinase and paxillin and promotes cell motility, via LPA1–3, in human pancreatic cancer," *Digestive Diseases and Sciences*, vol. 58, no. 12, pp. 3524–3533, 2013.

[118] K. Fukushima, K. Takahashi, E. Yamasaki et al., "Lysophosphatidic acid signaling via LPA_1 and LPA_3 regulates cellular functions during tumor progression in pancreatic cancer cells," *Experimental Cell Research*, vol. 352, no. 1, pp. 139–145, 2017.

[119] Y. Kishi, S. Okudaira, M. Tanaka et al., "Autotaxin is overexpressed in glioblastoma multiforme and contributes to cell motility of glioblastoma by converting lysophosphatidylcholine to lysophosphatidic acid," *The Journal of Biological Chemistry*, vol. 281, no. 25, pp. 17492–17500, 2006.

[120] H. Wang, H. Wang, W. Zhang, H. J. Huang, W. S. L. Liao, and G. N. Fuller, "Analysis of the activation status of Akt, NFκB, and Stat3 in human diffuse gliomas," *Laboratory Investigation*, vol. 84, no. 8, pp. 941–951, 2004.

[121] M. G. K. Benesch, Y. M. Ko, X. Tang et al., "Autotaxin is an inflammatory mediator and therapeutic target in thyroid cancer," *Endocrine-Related Cancer*, vol. 22, no. 4, pp. 593–607, 2015.

[122] S.-C. Su, X. Hu, P. A. Kenney et al., "Autotaxin–lysophosphatidic acid signaling axis mediates tumorigenesis and development of acquired resistance to sunitinib in renal cell carcinoma," *Clinical Cancer Research*, vol. 19, no. 23, pp. 6461–6472, 2013.

[123] E. S. Jeon, S. C. Heo, I. H. Lee et al., "Ovarian cancer-derived lysophosphatidic acid stimulates secretion of VEGF and stromal cell-derived factor-1α from human mesenchymal stem cells," *Experimental & Molecular Medicine*, vol. 42, no. 4, pp. 280–293, 2010.

[124] S. Liu, M. Murph, N. Panupinthu, and G. B. Mills, "ATX-LPA receptor axis in inflammation and cancer," *Cell Cycle*, vol. 8, no. 22, pp. 3695–3701, 2009.

[125] D. N. Brindley, F.-T. Lin, and G. J. Tigyi, "Role of the autotaxin–lysophosphatidate axis in cancer resistance to chemotherapy and radiotherapy," *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids*, vol. 1831, no. 1, pp. 74–85, 2013.

[126] B. P. C. Kok, G. Venkatraman, D. Capatos, and D. N. Brindley, "Unlike two peas in a pod: lipid phosphate phosphatases and phosphatidate phosphatases," *Chemical Reviews*, vol. 112, no. 10, pp. 5121–5146, 2012.

[127] M. G. K. Benesch, X. Tang, G. Venkatraman, R. T. Bekele, and D. N. Brindley, "Recent advances in targeting the autotaxin-lysophosphatidate-lipid phosphate phosphatase axis *in vivo*," *The Journal of Biomedical Research*, vol. 30, no. 4, pp. 272–284, 2016.

[128] N. Samadi, R. Bekele, D. Capatos, G. Venkatraman, M. Sariahmetoglu, and D. N. Brindley, "Regulation of lysophosphatidate signaling by autotaxin and lipid phosphate phosphatases with respect to tumor progression, angiogenesis, metastasis and chemo-resistance," *Biochimie*, vol. 93, no. 1, pp. 61–70, 2011.

[129] Y. Kihara, H. Mizuno, and J. Chun, "Lysophospholipid receptors in drug discovery," *Experimental Cell Research*, vol. 333, no. 2, pp. 171–177, 2015.

[130] D. Castagna, D. C. Budd, S. J. F. MacDonald, C. Jamieson, and A. J. B. Watson, "Development of autotaxin inhibitors: an overview of the patent and primary literature," *Journal of Medicinal Chemistry*, vol. 59, no. 12, pp. 5604–5621, 2016.

[131] S. Llona-Minguez, A. Ghassemian, and T. Helleday, "Lysophosphatidic acid receptor (LPAR) modulators: the current pharmacological toolbox," *Progress in Lipid Research*, vol. 58, pp. 51–75, 2015.

[132] J. L. Tanyi, Y. Hasegawa, R. Lapushin et al., "Role of decreased levels of lipid phosphate phosphatase-1 in accumulation of lysophosphatidic acid in ovarian cancer," *Clinical Cancer Research*, vol. 9, no. 10, Part 1, pp. 3534–3545, 2003.

[133] J. Gierse, A. Thorarensen, K. Beltey et al., "A novel autotaxin inhibitor reduces lysophosphatidic acid levels in plasma and the site of inflammation," *The Journal of Pharmacology and Experimental Therapeutics*, vol. 334, no. 1, pp. 310–317, 2010.

[134] S. R. Bhave, D. Y. A. Dadey, R. M. Karvas et al., "Autotaxin inhibition with PF-8380 enhances the radiosensitivity of human and murine glioblastoma cell lines," *Frontiers in Oncology*, vol. 3, p. 236, 2013.

[135] P.-D. St-Coeur, D. Ferguson, P. J. Morin, and M. Touaibia, "PF-8380 and closely related analogs: synthesis and structure-activity relationship towards autotaxin inhibition and glioma cell viability," *Archiv der Pharmazie*, vol. 346, no. 2, pp. 91–97, 2013.

[136] G. Venkatraman, M. G. K. Benesch, X. Tang, J. Dewald, T. P. W. McMullen, and D. N. Brindley, "Lysophosphatidate signaling stabilizes Nrf2 and increases the expression of genes involved in drug resistance and oxidative stress responses: implications for cancer treatment," *The FASEB Journal*, vol. 29, no. 3, pp. 772–785, 2015.

[137] N. Desroy, C. Housseman, X. Bock et al., "Discovery of 2-[[2-Ethyl-6-[4-[2-(3-hydroxyazetidin-1-yl)-2-oxoethyl]piperazin-1-yl]-8-methylimidazo[1,2-*a*]pyridin-3-yl]methylamino]-4-(4-fluorophenyl)thiazole-5-carbonitrile (GLPG1690), a first-in-class Autotaxin inhibitor undergoing clinical evaluation," *Journal of Medicinal Chemistry*, vol. 60, no. 9, pp. 3580–3590, 2017.

[138] *Study to Assess Safety, Tolerability, Pharmacokinetic and Pharmacodynamic Properties of GLPG1690*, 2017, https://clinicaltrials.gov/ct2/show/NCT02738801?term=GLPG1690&rank=2.

[139] *Safety and Efficacy of a Lysophosphatidic Acid Receptor Antagonist in Idiopathic Pulmonary Fibrosis*, https://clinicaltrials.gov/ct2/show/record/NCT01766817.

[140] *BMS-986020*, http://bciq.biocentury.com/products/am152.

[141] *Proof of Biological Activity of SAR100842 in Systemic Sclerosis*, 2016, https://clinicaltrials.gov/ct2/show/record/NCT01651143?term=SAR100842&rank=1.

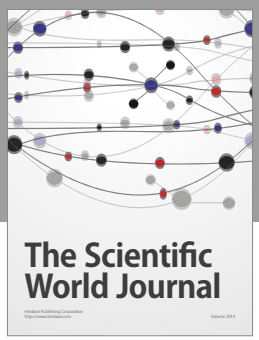
[142] I. Nikitopoulou, E. Kaffe, I. Sevastou et al., "A metabolically-stabilized phosphonate analog of lysophosphatidic acid attenuates collagen-induced arthritis," *PLoS One*, vol. 8, no. 7, article e70941, 2013.

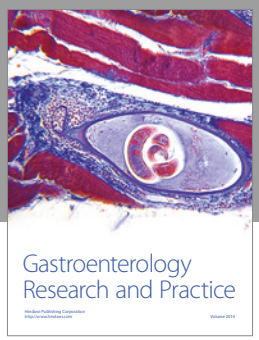
[143] H. Zhang, X. Xu, J. Gajewiak et al., "Dual activity lysophosphatidic acid receptor pan-antagonist/autotaxin inhibitor reduces breast cancer cell migration *in vitro* and causes tumor regression *in vivo*," *Cancer Research*, vol. 69, no. 13, pp. 5441–5449, 2009.

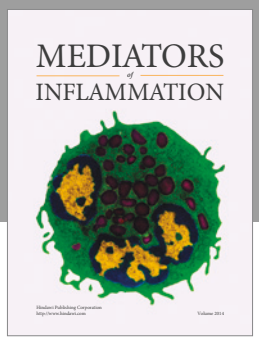
[144] M. Komachi, K. Sato, M. Tobo et al., "Orally active lysophosphatidic acid receptor antagonist attenuates pancreatic cancer invasion and metastasis *in vivo*," *Cancer Science*, vol. 103, no. 6, pp. 1099–1104, 2012.

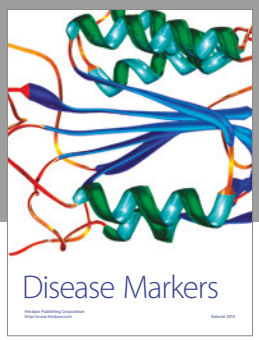
[145] S. M. Schleicher, D. K. Thotala, A. G. Linkous et al., "Autotaxin and LPA receptors represent potential molecular targets for the radiosensitization of murine glioma through effects on tumor vasculature," *PLoS One*, vol. 6, no. 7, article e22182, 2011.

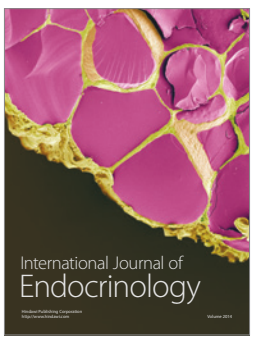
[146] N. Euer, M. Schwirzke, V. Evtimova et al., "Identification of genes associated with metastasis of mammary carcinoma in metastatic versus non-metastatic cell lines," *Anticancer Research*, vol. 22, no. 2A, pp. 733–740, 2002.

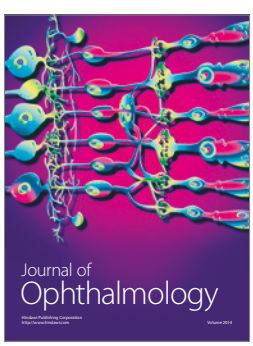


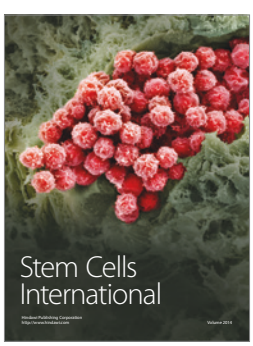


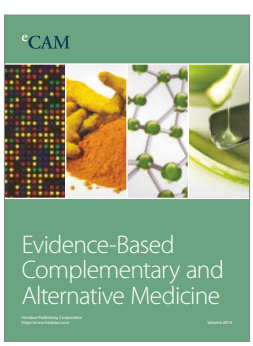


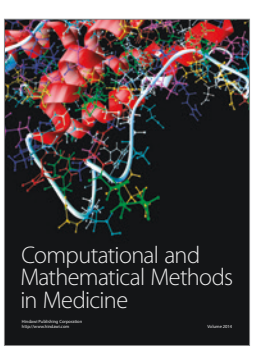


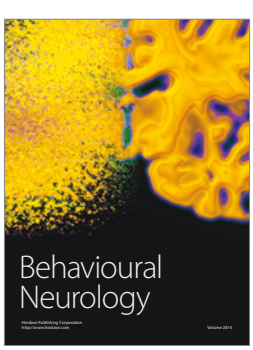


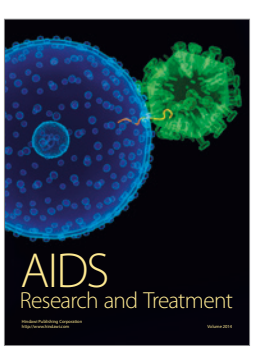


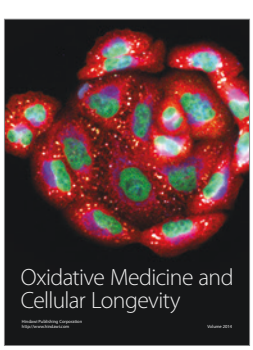










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