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Role of Autotaxin in Cancer Stem Cells

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Stem cells are a rare subpopulation defined by the potential to self-renew and differentiate into specific cell types. A population of stem-like cells has been reported to possess the ability of self-renewal, invasion, metastasis, and engraftment of distant tissues. This unique cell subpopulation has been designated as cancer stem cells (CSC). CSC were first identified in leukemia and the contributions of CSC to cancer progression have been reported in many different types of cancers. The cancer stem cell hypothesis attempts to explain tumor cell heterogeneity based on the existence of stem cell-like cells within solid tumors. The elimination of CSC is challenging for most human cancer types due to their heightened genetic instability and increased drug resistance. To combat these inherent abilities of CSC, multi-pronged strategies aimed at multiple aspects of CSC biology are increasingly being recognized as essential for a cure. One of the most challenging aspects of cancer biology is overcoming the chemotherapeutic resistance in CSC. Here, we provide an overview of autotaxin (ATX), lysophosphatidic acid (LPA), and their signaling pathways in CSC. Increasing evidence supports the role of ATX and LPA in cancer progression, metastasis, and therapeutic resistance. Several studies have demonstrated the ATX-LPA axis signaling in different cancers. This lipid mediator regulatory system is a novel potential therapeutic target in CSC. In this review, we summarize the evidence linking ATX-LPA signaling to CSC and its impact on cancer progression and metastasis. We also provide evidence for the efficacy of cancer therapy involving the pharmacological inhibition of this signaling pathway.

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CSC

An increasing body of evidence suggests that human cancers are comprised of heterogeneous populations of cells. The cancer stem cell hypothesis suggests that a subpopulation of tumor cells exhibits stem cell properties, such as self-renewal and multi-lineage differentiation [1] (**Figure 1**). The concept of CSC was first defined in acute myeloid leukemia [2,3]. Only a rare cell population could initiate tumorigenesis when transplanted into immunodeficient mice. Following these landmark studies, CSC has been identified in other types of tumors, including tumors of the brain, breast, head and neck, colon, lung, prostate, pancreas, liver, and ovary, and other types of hematologic malignancies [1,4-11]. CSC is thought to be capable of initiating drug resistance and recurrence due to their increased resistance to chemo- and radiation therapy responsible for the recurrence of cancer [1]. Also, a higher incidence of CSC correlates with more aggressive cancer progression and poorer outcome [4]. In addition to their ability to self-renew, the CSC population can also be identified using phenotypic surface markers and these populations are rare in most cancers [12].

A major limitation of the CSC model is that it views the tumor as a genetically homogeneous pool of cells, without considering their genetic heterogeneity, evolution, and selection for progressive growth. For example, if a tumor contains different sub-clones, some of these clones might appear to be virtually homogeneous populations because they are highly developed, yet they contain many and distinct types of mutations. Furthermore, these CSC are resistant to conventional therapies and may account for the relapse of the disease [13]. Various mechanisms are implicated in the evasion of CSC from therapy, including increased DNA damage repair, resistance to apoptosis, altered cell cycle checkpoint control, and overexpression of multi-drug-resistant proteins [14].

In addition, cancer cells also display metabolic abnormalities [15]. Cancer cells preferentially rely on a high rate of glycolysis in the presence of oxygen, a phenomenon known as aerobic glycolysis [16]. The metabolic pathways in CSC, however, have not been fully characterized. CSC from different cancer types may have distinct metabolic requirements [17]. Inhibition of anaerobic glycolysis does not impair the clonogenic potential of glioma CSC [18] and disrupting mitochondrial metabolism impacts ovarian CSC [19]. CSC appears to be more versatile in terms of metabolic dependency. Metabolic targeting in CSC has to be designed based on the specific metabolic needs of individual cancer. Recent research has begun to uncover the roles of microRNAs in cancer and CSC [20-23]. Dysregulated microRNAs have been implicated in CSC function and tumorigenesis.

A better understanding of the properties of CSC within tumors should provide insight into the most important cells that can drive sequential rounds of tumor growth. CSC is equipped with innate machinery that protects them from radiation and chemotherapy within the tumor microenvironment. More effective therapies will require deeper insight into the signaling mechanism involving the self-renewal and drug resistance of CSC.

Physiological functions of the LPA-ATX axis

LPA is a bioactive phospholipid that stimulates the proliferation, migration, and survival of many cell types [24]. LPA has no membrane-perturbing effects and is water-soluble [25]. Six G-coupled LPA receptors (LPA1-6) have been identified (**Figure 2**). They have a broad tissue distribution and overlapping signaling properties [26], and LPA activates these receptors through heterotrimeric G α proteins (G $\alpha_{12/13}$ (LPA1-2 and LPA4-6), G α_q (LPA1-5), G α_i (LPA1-4 and LPA6), and G α_s (LPA4 and LPA6)) [27,28]. LPA1–3 receptors belong to the EDG family of G protein-coupled receptors and LPA4–6 receptors are related to the purinergic P2Y receptor family [29].

ATX, a member of the ectonucleotide pyrophosphate and phosphatase (ENPP) family, primarily catalyzes the hydrolysis of lysophosphatidylcholine, resulting in LPA production [26,30]. ATX was originally identified as an autocrine motility factor in human melanoma cells [31] and has lysophospholipase D activity [31,32]. ATX is naturally expressed in multiple tissues with the highest mRNA levels detected in the nervous system, placenta, ovary, intestine, and high endothelial venules with moderate levels of expression in the kidney, prostate, testis, colon, lung, and pancreas [33-35]. ATX activity has also been detected in cerebrospinal fluid, plasma, serum, and peritoneal fluid [34]. ATX functions in LPA production in extracellular fluids [26]. Secretion of ATX leads to a high concentration of ATX in cerebrospinal fluid and in the high endothelial venules of lymphoid organs [36-38]. ATX is essential for early embryological development in mice [39-41]. Genetic deletion of ATX (encoded by *Enpp2*) in mice (*Enpp2*^{-/-}) caused death at E9.5 with obvious vascular and neural tube defects. In addition, these mice have a poorly formed yolk sac vascular network, as well as enlarged embryonic vessels, malformed allantois, reduced axial turning, kinked neural tube, and an asymmetric neural head fold. ATX heterozygous knockout mice are viable, but they develop pulmonary hypertension and have a 50 % reduction in LPA plasma levels compared with wild-type mice. Collectively, ATX is essential for vascular development and this activity is responsible for the correct concentration of LPA in plasma.

ATX-LPA signaling pathway—critical new player in CSC

The ATX-LPA signaling pathway is physiologically relevant during development and adulthood. Dysregulation of this axis is linked to several pathologies, including rheumatoid arthritis, fibrosis, neuropathic pain, and cancer [27]. LPA has been reported to stimulate proliferation, invasion, metastasis, and therapeutic resistance in various cancers, such as ovarian, prostate, breast, melanoma, thyroid, and intestinal cancers [25], and LPA levels in the serum are increased in multiple myeloma (MM) patients [42]. Moreover, LPA acts in an autocrine manner with ovarian cancer cells [43]. The classic LPA receptors were involved in tumor angiogenesis, migration, invasion, and metastasis [44-47]. The mechanisms include stimulation of vascular endothelial growth factor production [44,48,49] and activation of several signaling pathways, such as the RAS/RAF1/MEK/ERK pathway [50,51], RHOA/RHO associated kinase pathway [52], PI3K/AKT pathway [53], WNT/ β -Catenin pathway [54], p38/MAPK pathway [46], PKC α /CARMA pathway [47], and EGFR signaling pathway [55]. Overexpression of LPA1 receptor in MDA-MB-231 cells enhances

tumor growth and promotes bone metastasis [56]. Further, overexpression of LPA1, LPA2, and LPA4 receptors in mouse embryonic fibroblasts (MEFs) induces cell transformation and tumor formation [57]. LPA2 is overexpressed in various common cancers, including ovarian, colon, gastric, and invasive ductal breast carcinoma [58], and *Lpa2*^{-/-} mice show decreased tumor incidence and progression of colon adenocarcinomas [59]. Furthermore, overexpression of LPA1, LPA2, and LPA3 receptors under the control of the mouse mammary tumor virus long terminal repeat promoter results in metastatic mammary carcinomas [60]. In addition, in ovarian cancer cells, LPA treatment stimulates the expression of CSC-associated genes, including *OCT4*, *SOX2*, *ALDH1*, and drug transporters [61]. Moreover, LPA promotes CSC-like characteristics, such as sphere-forming ability, resistance to anti-cancer drugs, and tumorigenic potential in xenograft transplantation. Knockdown or pharmacological inhibition of LPA1 reduces the LPA-stimulated proliferation and acquisition of CSC-like properties in ovarian cancer cells. These results suggest that LPA plays a key role in the self-renewal, therapeutic resistance, and metastasis of ovarian CSC.

In recent years, the ATX-LPA signaling pathway has been implicated in several aspects of cancer cell biology that include cancer growth, invasion, metastasis, and therapeutic resistance [28]. The ATX expression is elevated in many types of cancers, such as neuroblastoma, glioblastoma, hepatocarcinoma, B-cell lymphoma, melanoma, renal, thyroid, breast, and non-small cell lung cancers [30,62-67]. Also, the ATX copy number is amplified in 10–20% of some cancers [35]. The mechanisms of control of ATX expression are complex and not fully understood. Overexpression of ATX does not induce tumorigenesis, whereas the combination of ATX expression with Ras transformation promotes tumor aggressiveness and metastasis [68], suggesting a pivotal role of ATX in the acquisition of metastatic potential. Consistent with the LPA-stimulated self-renewal of ovarian CSC, ATX has been found to play an important role in the maintenance and proliferation of ovarian cancer stem cells [61]. ATX was demonstrated to be highly expressed in sphereforming CSC-like populations of ovarian cancer cell lines and primary ovarian CSC isolated from patients [61]. Moreover, ovarian CSC produced high levels of LPA via an ATX-dependent mechanism, and knockdown or pharmacological inhibition of ATX markedly attenuated the LPA-producing, tumorigenic, and drug resistance potentials of ovarian CSC. Consistently, ATX inhibitors reduced melanoma metastasis and chemoresistance of breast CSC [69]. These results suggest that ATX-LPA signaling axis plays a pivotal role in the tumorigenic, drug-resistance, and metastatic potentials of CSC.

LPA and the tumor microenvironment

There are many non-tumor cell elements, such as endothelial cells, fibroblasts, infiltrating immune cells, and extracellular matrix associated with tumors (**Figure 3**). These are referred to as the tumor microenvironment [70]. The tumor microenvironment around tumor cells influences the function of the cells, resulting in significant variation in cellular function [71,72]. The complexity of the tumor microenvironment is amplified due to crosstalk between tumor cells and the tumor microenvironment [73]. The tumor microenvironment plays a role in adaptive drug resistance and is linked to therapy failure and tumor recurrence [70]. Recent studies have suggested that the inflammatory cytokines and chemokines from

breast cancer cells induce ATX in tumor-associated fibroblasts and adipocytes, which increases breast cancer progression [74,75]. LPA has also been implicated in epithelial-to-mesenchymal transitions that facilitate cancer cell spread beyond the primary tumor [35]. LPA receptors are ubiquitously expressed in stromal cells of the lung microenvironment [76]. The LPA1 receptor is predominantly expressed in lung fibroblasts, and the LPA2, LPA4, and LPA5 receptors are expressed in alveolar macrophages. Interestingly, lung metastasis was abolished in *Lpa5^{-/-}* mice [77]. In addition, LPA1 and LPA3 receptors in stromal cells promote growth and metastasis of MM cells [78], suggesting a pivotal role of LPA in the regulation of tumor microenvironment.

Accumulating evidence suggests that mesenchymal stem cells (MSC) promote *in vivo* growth of xenograft transplanted tumors [79,80]. Cancer-derived LPA stimulates the differentiation of human MSC to myofibroblast-like cells [81]. Moreover, LPA promotes the secretion of pro-angiogenic cytokines, vascular endothelial growth factor, and stromal cell-derived factor-1 (also known as CXCL12) from MSC [82]. Proteomic analysis of LPA-conditioned medium derived from A549 lung adenocarcinoma identified β ig-h3 and periostin as LPA-induced secreted proteins [83,84]. Both β ig-h3 and periostin have been implicated in tumorigenesis via the regulation of the tumor microenvironment [85,86]. Periostin is an extracellular matrix protein that is expressed in injured tissues. It promotes angiogenesis and tissue repair [87,88] and is a prognostic marker in ovarian cancer patients [89]. Furthermore, periostin has been observed in the cancer-associated stroma in the lung and colon [90-92] and reportedly supports the adhesion of cancer cells, including ovarian, breast, and colon cells [93-95]. Periostin in stromal cells induces bone metastases from breast cancer [96]. Silencing of periostin expression in MSC can abrogate the MSC-stimulated tumor growth *in vivo* [83]. In addition, stromal fibroblast-expressed periostin is required for metastatic colonization of metastatic CSC by recruiting WNT ligands [97]. The collective findings suggest that an understanding of stromal LPA receptors, LPA, ATX, and periostin in the tumor microenvironment is equally as important as studying the tumor cell ATX-LPA axis.

Development of inhibitors against the ATX-LPA signaling axis for CSC-targeted therapy

The LPA signaling pathways are involved in many aspects of angiogenesis [98,99], metabolic processes [100-103], and immune system function [104]. Several studies are underway to access the therapeutic potential of ATX inhibitor and/or LPA receptor antagonists. Targeting LPA receptor using biological agents (i.e. RNA silencers) has resulted in a reduction of tumor growth [77]. Knockdown of LPA2 or LPA3 receptors using RNA interference can reduce the tumor burden in xenografted colon cancers. The pharmacological LPA receptor inhibitor, Ki16425, is an antagonist targeting LPA1 and LPA3 receptors. Ki16425 was reportedly able to significantly reduce pancreatic cancer development [105] and reduce hepatocarcinoma tumor cell invasion and lung metastases [77]. Furthermore, Ki16452 can significantly reduce LPA-related HCC cell invasion [106]. Moreover, silencing of LPA1 or treatment with Ki1625 was demonstrated to lead to the inhibition of sphere-forming ability, tumorigenicity, and drug resistance in ovarian CSC [61]. Taken together,

these findings indicate that blocking LPA production and/or signaling may block the tumor growth and metastasis by targeting CSC.

Among the ATX inhibitors, small non-lipid molecule inhibitors tend to have better oral bioavailability [107]. PF-8380 is a piperazinylbenzoxazolone derivative that was the first compound shown to reduce plasma LPA levels *in vivo* [108], abrogate radiation-induced AKT activation, and decrease tumor vascularity and tumor growth [109]. ONO-8430506, a tetrahydrocarboline derivative and ATX inhibitor, has been used to suppress plasma ATX activity in mice [110]. In another study, S32826, a benzyl phosphonic acid derivative ATX inhibitor, was used to reduce chemical liver carcinogenesis [111]. In other studies, *α*-bromophosphonates (BrP-LPA), which are lipid-mimetic ATX inhibitors and pan-antagonists of LPA1-3 receptors, were used to reduce breast tumor growth in orthotopic xenograft models [112] and lung cancer metastasis in nude mice [113]. BrP-LPA treatment in murine glioma models affects the tumor vasculature [114]. Pharmacological inhibition or knockdown of periostin can block proliferation of drug-resistant cells by reducing the expression of CSC-associated genes, including *OCT4*, *SOX2*, *ALDH1A1*, and those encoding ABC transporters. Moreover, compound 3b, an ATX inhibitor derived by lead optimization of the benzene-sulfonamide *in silico* hit compound 3, was reported to potentially reduce the drug resistance of breast CSC [69]. These results suggest the potential of ATX inhibitors in cancer therapy by targeting therapy-resistant CSC. Ongoing studies are aimed at understanding the potential therapeutic effects of specifically designed drugs to target ATX-LPA pathways.

Conclusions and future directions

CSC is at the top of a tumor cell hierarchy participating in tumor initiation and the progression of many tumors. CSC has the potential for self-renewal and repopulating the tumor population, like normal stem cells. CSC are more quiescent than the bulk of tumor cells and are less sensitive to therapies. Thus, effective anti-cancer therapy not only requires the elimination of the bulk of tumor mass but also depends on eradication of CSC.

Recent findings on the role of ATX in cancer progression and metastasis have highlighted a new functional contribution for the microenvironment. In this review, we provide an overview of the pivotal roles of the ATX-LPA signaling axis in the self-renewal, tumorigenic, drug resistance, and metastatic potentials of CSC. Inhibition of the signaling axis is a potential cancer therapy that targets therapy-resistant CSC. The results described in this review suggest that targeting ATX has therapeutic benefits for clinical application. However, challenges remain. ATX-LPA axis signaling pathways are involved in distinct G protein-coupled receptors, inflammatory cytokine pathways, and transactivation of receptor tyrosine kinase signaling in cancer. Thus, efforts should be made to define additional molecular biomarkers linked to specific LPA, LPA receptors, and ATX activities that may provide new pharmacologic targeting opportunities.

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Abbreviations:

ATX	autotaxin
CSC	cancer stem cells
LPA	lysophosphatidic acid

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Figure 1.
Hypothetic model for cancer stem cells. Cancers are composed of heterogeneous cell populations.

Figure 2.
Overview of autotaxin-lysophosphatidic acid signaling.

Figure 3.
ATX-LPA signaling in tumor microenvironment.