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Review Article

Autotaxin-LPA receptor axis in the pathogenesis of lung diseases

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Abstract: Lysophosphatidic acid (LPA) is a small lipid which mediates a variety of cellular functions via the activation of LPA receptors. LPA is generated from lysophosphatidylcholine by the extracellular enzyme, autotaxin (ATX). Elevated ATX expression, LPA production and their signaling pathways have been reported in multiple pathological conditions of lung tissue, including inflammation, fibrosis and cancer. Emerging evidence has highlighted the importance of ATX and LPA receptors in the pathogenesis of lung diseases. Here, we briefly review the current knowledge of different roles of the ATX-LPA receptor axis in lung diseases focusing on inflammation, fibrosis and cancer.

Keywords: Lysophosphatidic acid receptor, autotaxin, lung diseases

Introduction

Lysophosphatidic acid (LPA) is a small, naturally occurring active lipid which is present in blood plasma as well as in all eukaryotic tissues [1, 2]. LPA is generated from lysophosphatidylcholine (LPC) by extracellular autotoxin (ATX), also known as lysophospholipase D [3]. ATX is present in plasma, follicular fluid, saliva, and malignant effusions [4]. To date, seven LPA receptors have so far been identified, namely LPA1-LPA7 [1, 5]. These receptors are all rhodopsin-like G protein-coupled receptors (GPCRs) that differ in their tissue distribution and downstream signaling pathways. Through binding with distinct cell surface receptors, LPA exhibits a wide range of biological effects on a variety of cell types, including epithelial cells, fibroblasts, lymphocytes, and smooth muscle cells [6-8]. LPA controls basic physiological processes by activating cell proliferation [9], differentiation and migration [10], maintaining fluid homeostasis [11], and promoting wound healing [12]. Accumulating evidence has shown ATX and LPA receptors are aberrantly expressed in pathological conditions. Thus, the ATX-LPA receptor axis is becoming increasingly recognized as an important contributor to a variety of pathological processes, including chronic inflammation,

fibrosis, colitis and cancer [13-15]. For instance, ATX expression has been shown to be increased in many types of cancer cells and in tissues with chronic inflammation [16]. Further, the expression of LPA2 receptor is enhanced in numerous types of tumors [17, 18].

Over the past decade, the role of ATX and LPA receptors in the pathogenesis of lung diseases has been subjected to extensive examination. An increasing line of evidence is emerging, which elucidates important roles of the ATX-LPA receptor axis in the development and/or progression of pulmonary fibrosis, inflammation and cancer. In this review, we will discuss recent findings of the specific roles and mechanisms of ATX and LPA receptors in the pathogenesis of lung diseases.

The role of ATX-LPA2 axis in lung inflammation

The inflammatory response of the lung to pathogens, toxins, pollutants, irritants, and allergens is complex and involves a variety of mechanisms. Acute inflammation is usually seen in pneumonia and acute respiratory distress syndrome (ARDS), and chronic inflammation is represented by chronic obstructive pulmonary disease (COPD) and asthma [19]. During inflamma-

tion, numerous types of inflammatory cells including dendritic cells, macrophages, neutrophils, lymphocytes, eosinophils, and epithelial cells are activated to defend against pathogens and repair tissue. Activated lymphocytes release cytokines and mediators to modify the activity of other inflammatory cells. LPA is one of the biological mediators whose expression is enhanced during inflammations, including lung inflammation. An earlier report by Georas and co-workers demonstrated that LPA is detectable in human bronchoalveolar lavage (BAL) fluids at basal conditions and is increased in response to segmental allergen challenges [20]. A later study demonstrated in a murine asthma model that there is approximately 2.8 fold increase of LPA production in the BAL fluid of affected animals [21]. Moreover, they found that LPA2^{+/-} mice, but not LPA1^{+/-} mice, exposed to *Schistosoma mansoni* egg revealed significantly reduced cell number and eosinophils in BAL fluids, compared to challenged wild type mice. LPA species can vary in length and fatty acid saturation, and the major forms of LPA, which are increased in allergic inflammation, are the 18:1, 20:4, 22:5, and 22:6 species. More recently, the Christman group showed that the LPA species, 22:5 and 22:6, are the major forms increased in the BAL fluids in human patients with asthma [22].

The concentration of ATX protein in the BAL fluids is significantly enhanced during allergic inflammation. In rodent models, it has been shown that blocking ATX activity produced a marked attenuation of allergic lung inflammation [22]. These findings have thus demonstrated that the ATX-LPA2 axis plays a critical role in the development of allergic lung inflammation. Previous evidence has shown that LPA enhances the expression and secretion of IL-8 in airway epithelial cells in both human and murine model [23]. IL-8 could further promote neutrophil migration during lung inflammation. However, it remains elusive as to whether IL-8 expression is induced by LPA via LPA2 receptor and further, it has yet to be identified which type(s) of cells in the lungs are the major source of LPA2 and IL-8 expression. Future studies are also required to address what is the main source of ATX in the lung during inflammation. Previous report by Yang et al. demonstrated that ATX is expressed in the basal cells of bronchial epithelium and even higher expression is exhibited in stromal B lymphocytes [24]. It is

likely that the increased abundance of ATX during lung inflammation is due to an increase in the number of B lymphocyte in inflamed lung, although further experimental confirmation is needed.

The role of ATX-LPA1 axis in lung fibrosis

In the lung, aberrant wound-healing process in response to injury is thought to be one of the main factors contributing to idiopathic pulmonary fibrosis (IPF) [25]. IPF and other fibrotic lung diseases are associated with high morbidity and mortality. In lung fibrosis, fibroblasts migrate into the fibrin-rich exudates under the induction by airspace fibroblast chemoattractant. It has been widely accepted that inhibition of fibroblast migration attenuates pulmonary fibrosis [26]. LPA has been recently identified as a mediator of fibroblast chemoattractant activity in the airspaces of bleomycin-induced lung fibrosis mouse model. In that study, the authors demonstrated that LPA acting through the LPA1 receptor mediates lung fibroblast migration [27]. They showed that LPA1-deficient mice challenged with bleomycin are more resistant to developing pulmonary fibrosis. Specifically, accumulation of fibroblasts and vascular leak were both markedly attenuated in LPA1-deficient mice, following the bleomycin challenge. Moreover, it was shown that LPA levels were elevated in BAL samples from individuals with IPF and the fibroblast chemotactic activity was dependent on fibroblast LPA1 receptor. This study provided the first evidence that LPA1 represents a crucial link between lung injury and pulmonary fibrosis. A later study from a different group further demonstrated that an orally active LPA1 receptor antagonist AM966 reduced lung injury, vascular leakage, inflammation and fibrosis following intratracheal bleomycin instillation in mice [28].

More recently, Tang and co-workers showed that, in addition to stimulatory effects on local fibroblasts, LPA via LPA1 receptor could also mediate bone-marrow derived-mesenchymal stem cells (BMSCs) differentiation and their secretion of extracellular matrix proteins in the lung tissue [29]. They showed that LPA1 antagonist, Antalpa1, attenuated bleomycin-induced transdifferentiation of BMSCs and ECM expression and the resultant pulmonary fibrosis. Clinically, lung fibrosis is a common complication of radiation therapy for lung cancer. Work

from the Jiang's group demonstrated that inhibition of the LPA-LPA1/3 signaling pathway with VPC12249 attenuated the development of lung fibrosis caused by radiation [30]. They showed that VPC12249 administration in mice downregulated the expression of transforming growth factor β 1 (TGF- β 1) and connective tissue growth factor (CTGF). This study revealed that, mechanistically, LPA acting on LPA1/3 receptor promotes fibroblast proliferation and extracellular matrix protein expression by upregulating the expression of TGF- β 1 and CTGF in lung fibroblasts. As VPC12249 inhibits both LPA1 and LPA3 receptors, it is unclear whether LPA3 receptor plays a role in radiation induced pulmonary fibrosis. Combined, this evidence demonstrates that the LPA-LPA1/3 signaling pathway plays a critical role in the pathogenesis of pulmonary fibrosis. On the other hand, a recent study by the Natarajan group showed that LPA2 deficiency confers protection against bleomycin-induced lung injury and fibrosis in mice [31]. They observed that knock-down of LPA2 but not LPA1 in cultured human lung fibroblasts attenuated the LPA-induced expression of TGF- β 1, α -SMA, and ECM proteins, which are important factors in promoting tissue fibrosis. It is possible that LPA1 and LPA2 receptors, through different signaling pathways, play differential and additive roles in the pathogenesis of lung fibrosis.

Given the LPA-generating role of ATX, it would not be surprising that increase of ATX expression in the lung would promote lung fibrosis through the LPA-LPA1/2/3 axis. Interestingly, it was found that ATX induced lung epithelial cell migration through both LPA-dependent and -independent pathways [32]. It was shown in this study that ATX not only induces cell migration via LPA-PKC δ -cortactin pathway but also promotes lung epithelial cell migration through interactions with LPA1 receptor and integrin β 4 complex on the cell surface. As fibroblast cell migration is a critical step in the pathogenesis of lung fibrosis, it would be important to understand whether lung fibroblasts express ATX, thereby facilitating fibroblast cell migration. In fact, recent evidence shows that ATX is upregulated in synovial fibroblasts in mouse models of arthritis [33].

The role of ATX in lung cancer

ATX was first identified as an autocrine motility-stimulating factor using a human melanoma

cell line [34], and later found to be abundantly expressed in numerous tumor cell species [35]. The first evidence that ATX might promote cell proliferation in lung cancer is from the Tsao group in 1999 [24]. They determined ATX mRNA expression in normal human bronchial epithelial cells and non-small-cell lung cancer cell lines and found that ATX was overexpressed in all histological subtypes of lung tumor cell lines, including squamous cell carcinoma, adenocarcinoma, adenosquamous carcinomas, and large cell carcinoma. In lung tissue, ATX expression is higher in poorly differentiated tumor cells, whereas much lower expression is observed in well or moderately differentiated tumor cells. The Tsao group also provided the first evidence that ATX is highly expressed in adjacent B lymphocytes in lung cancer tissue. This renders one to suspect whether the increased abundance of ATX in BAL during lung inflammation is actually due to the increase of local B lymphocyte number.

A recent report has further demonstrated that ATX plays a critical role in promoting lung tumor cell growth. Using an engineered three-dimensional tumor xenograft model of non-small-cell lung cancer in nude mice, Xu and co-workers observed that administration of Brp-LPA, an inhibitor of lysophospholipase D activity of ATX and a pan-antagonist of LPA receptors, dramatically inhibited tumor growth [36]. Treatment with Brp-LPA has also suppressed tumor cell migration and invasion. This study implicates a critical role of the ATX-LPA receptor pathway in lung tumor cell proliferation or tumor growth. However, it is not known which LPA receptor(s) is pivotal for lung tumor cell growth. A recent study demonstrated that LPA1 is required for LPA to stimulate lung cancer cell growth through induction of ADAM12 protein in A549 human lung adenocarcinoma cells [37]. Moreover, the LPA1 receptor is well known to be a pro-migration factor in many different cell types. LPA1 receptor expression has been linked to the motility and invasiveness of several metastatic cell lines [38]. For instance, LPA1 promotes breast carcinoma cell metastasis to the bone and silencing of LPA1 expression significantly reduces the progression of bone metastases [39]. It would be important to understand if lung cancer cell migration or metastases requires the presence of LPA1. On the other hand, it has been reported that the expression of LPA2 receptor was elevated in ovarian,

breast and colorectal cancer cells [17, 18]. It is possible that LPA2 receptor might be responsible for the LPA-mediated cell proliferation in lung cancer, although experimental evidence is required to validate this possibility. Very recently, LPA5 gene was found to be unmethylated, eliciting increased expression in lung-derived adenocarcinoma RLCNR cells, suggesting that increased LPA5 expression may also be involved in promoting growth in lung tumor cells [40]. Interestingly, another study from the same group observed a decreased expression of LPA3 in RLCNR cells and that overexpression of LPA3 significantly attenuated migration of RLCNR cells [41], suggesting a protective role of LPA3 in the progression of lung cancer.

Perspectives

Together, the data highlighted in this review illustrates the importance of LPA receptors in lung inflammation, fibrosis and cancer. However, further work must be performed in order to determine the specific role and underlying mechanisms of how each receptor may be contributing toward the pathogenesis of these diseases. Future work in this field could promote the development of novel therapeutic targets against lung cancer, inflammation and fibrosis. It is important to note that the regulation of autotoxin, the enzyme upstream of LPA receptor mediated cellular signaling, has not been well addressed in lung pathophysiology. A better understanding of the source of autotoxin secretion in local lung tissue will provide an important clue in lung disease treatment. In fact, targeting autotoxin in the treatment of chronic inflammation and cancer has long been proposed, with pharmaceutical companies now developing autotoxin enzyme inhibitors for future clinical use. Therefore, further work on the role and molecular mechanisms of the autotoxin-LPA receptor axis mediated changes in the lung will shed novel light on the treatment of pulmonary diseases.

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Disclosure of conflict of interest

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