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LPA and Autotaxin: Potential drug targets in asthma?

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Abstract

Lysophosphatidic acid (LPA) is a versatile lysolipid, and activates a variety of signaling cascades in many cell types. Extracellular LPA is produced from lysophosphatidylcholine (LPC) by the enzyme autotaxin (ATX), and binds to a family of G-protein coupled receptors on its target cells. Research by many groups continues to support the idea that LPA, and the ATX-LPA axis, have important roles in asthma and allergic airway inflammation. In vitro studies have shown that LPA activates many cell types implicated in airway inflammation, including eosinophils, mast cells, dendritic cells, lymphocytes, airway epithelial cells, and airway smooth muscle cells. In animal models ATX and LPA receptor antagonists have been shown to attenuate allergic airway inflammation and hyperreactivity, cardinal features of asthma in humans. ATX and LPA antagonists are currently under active development to treat lung fibrosis, cancer, and other conditions. If compounds with acceptable safety profiles can be identified, then it seems likely that they will be useful in inflammatory lung diseases like asthma.

Keywords

Lysophosphatidic acid; ATX; Asthma; LPA drug targets; Autotaxin

A personal story and debt of gratitude to Dr. Viswanathan Natarajan

After completing my fellowship in Pulmonary and Critical Care Medicine at Johns Hopkins University in 1994, I joined the faculty and launched my own lab studying the regulation of cytokine gene expression in T lymphocytes. This was soon after the discovery of Th1 and Th2 subsets by Mosmann and Coffman (1), and the idea that allergic diseases like asthma were caused by dysregulated expression of Th2 cytokines such as IL-4, IL-5 and IL-13 was starting to take hold. I was fortunate to obtain an NIH K08 award that helped me launch my career as an independent researcher. The aim of the K08 award were to identify regulatory DNA elements that controlled the expression of the interleukin-4 (IL-4) gene. To accomplish this, I used standard approaches at that time, which involved making promoter reporter constructs that we transfected into T cell lines, followed by analysis of reporter activity using different assays. We complemented these functional studies with gel shift assays, trying to identify the nuclear transcription factors that bound to different DNA elements.

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The Johns Hopkins Pulmonary Division at that time housed the labs of dozens of faculty members conducting research in a variety of areas, and we had a communal kitchen with coffee machine, where I had a habit of stopping for a mid-afternoon cup of coffee. Luckily for me, Dr. Viswanathan Natarajan (Nati) also needed a mid-afternoon caffeine boost, and we soon started interacting regularly and talking science in this informal setting. I didn't realize at the time that I was learning from a world-renowned lipid biochemist! During one of these meetings, Nati shared an article from the Journal of Immunology showing that human T cells expressed receptors for lysophosphatidic acid (LPA), which inhibited secretion of interleukin-2 (IL-2), an important cytokine for T cell function (2). I had never heard of LPA before, and started reading about this interesting lipid compound. The more I read about LPA, the more intrigued I became about its potential role in regulating immune responses. Nati gave me a vial of LPA and instructions about how to use this in cell culture experiments. Interestingly, we found that LPA had an enhancing effect on IL-13 gene expression in T cells, especially under conditions of sub-maximal activation (3). Soon thereafter, working with Nati and the incredibly talented Dr. Evgeny Berdyshev and pulmonologist Dr. Mark Liu, we reported that LPA was constitutively present in bronchoalveolar lavage (BAL) fluids from human subjects, but significantly increased following segmental allergen challenge (4). These studies launched my decades-long interest in how LPA impacts allergic immune responses and airway inflammation in asthma that I continue to study to this day. During this process, I have been fortunate to benefit from Nati's wisdom, guidance, and mentorship. Nati was unfailingly upbeat and encouraging, and always willing to share advice and reagents. He was instrumental in helping me establish new collaborations and mouse models that allowed me to obtain funding and continue to publish in this area. He is a true role model and was an inspiration to a generation of young scientists. I cherish my decades-long friendship with Nati and Lakshmi, and wish him the best during his well-deserved retirement!

Current thinking about the role of LPA and ATX in asthma

Extracellular LPA is produced from lysophosphatidylcholine (LPC) by the enzyme autotaxin (ATX), and binds to a family of G-protein coupled receptors on its target cells (LPA1-6). Research by many groups continues to support the idea that LPA, and the ATX-LPA axis, have important roles in asthma and allergic airway inflammation. The potential role of LPA in asthma and inflammatory lung diseases was recently comprehensively reviewed (5–7). Here, I will briefly summarize previous data and highlight recent studies which have provided new insights in this area. In broad terms, LPA might contribute to asthma pathogenesis in two areas. First, LPA might promote allergic airway inflammation, by activating or recruiting pro-inflammatory cells. Second, LPA, acting on airway smooth muscle (ASM) and other structural cells in the lung, could enhance airway hyperreactivity (AHR). These possibilities are not mutually exclusive, and future research studies using specific receptor antagonists in clinical research studies should be revealing in this regard.

LPA and airway inflammation in asthma

Pre-clinical data demonstrate that LPA acts on many cell types implicated in airway inflammation, including eosinophils, mast cells, dendritic cells, lymphocytes, and airway

epithelial cells (reviewed in (5–7)). LPA is also now known to be an important regulator of lymphocyte motility and trafficking in lymph nodes, by engaging LPA2 on T cells and other receptors on endothelial cells (8, 9). Most *in vitro* studies demonstrate that LPA can activate cells, or induce their motility or migration on specific substrates, suggesting that LPA has a pro-inflammatory effect *in vivo*. However, LPA can also dampen inflammatory signals in some contexts (10, 11). Although LPA can enhance T cell production of the pro-inflammatory cytokine IL-13 (3, 12), LPA also inhibits the function of cytotoxic CD8+ T cells via LPA5 (13). Taken together, these results suggest that the net effects of LPA will depend on the tissues in which it is expressed, and receptors engaged on target cells.

Experiments using pathway antagonists have provided support for the idea that ATX and LPA contribute to airway inflammation and AHR in animal models of asthma. An early paper in this regard was reported by Park et al (collaborating with Dr. Natarajan) (14), who showed that a small molecule ATX inhibitor (GWJ) attenuated airway inflammation in a mouse allergen challenge model. Because allergic airway inflammation was also attenuated in LPA2 knock-out mice, similar to previous results of Dr. Yutong Zhao and Dr. Natarajan (15), Park et al speculated that the pro-inflammatory effects of LPA were mediated by LPA2. Further support for a pro-inflammatory role for LPA2 comes from the recent report by Kondo et al (12), who demonstrated that the LPA2 antagonist H2L5186303 inhibited T cell IL-13 production and airway inflammation in a mouse model of house dust mite (HDM) induced asthma. Although these studies suggest that LPA2 would be an attractive therapeutic target in asthma, we found that HDM-induced allergic airway inflammation was actually inhibited by the LPA2 *agonist* DBIBB (16). Therefore, more research is needed to refine the precise LPA receptors involved in models of allergen-driven airway inflammation and hyperreactivity. One interesting possibility is that during repetitive cycles of airway inflammation and repair, locally produced LPA might promote airway fibrosis and remodeling. This would be in keeping with the known ability of LPA to activate fibroblasts and pro-fibrotic signaling cascades (17–19).

LPA and airway hyperreactivity in asthma

Separate from its potential effects on airway inflammation or remodeling, LPA might directly regulate AHR. AHR refers to the tendency of airways to constrict in response to inhaled irritants, and is the defining feature of asthma. The pathogenesis of AHR in asthma is complex, and involves enhanced airway smooth muscle (ASM) cell contractility, and alterations in airway innervation and structure, leading to airflow limitation (20). ASM constriction and expiratory flow limitation in turn cause the characteristic signs and symptoms of asthma including wheezing, chest tightness, and shortness of breath. There are several potential mechanisms by which LPA might promote AHR. First, pioneering studies by Toews and others showed that LPA directly enhances ASM growth and contractility (21–23). Second, by inducing airway wall edema or excess mucus production, LPA could cause narrowing of the airway luminal diameter, rendering airways further susceptible to ASM induced closure. Third, Jendzjowsky and colleagues recently reported a critical role for LPA in causing acute bronchoconstriction in the ovalbumin (Ova) sensitized Brown Norway rat model. These authors identified a novel neurogenic mechanism involving carotid

body induced stimulation of the vagus nerve, initiated by activation of LPA receptors and TRPV1 receptors within the carotid body (24).

Taken together, substantial evidence now supports the idea that ATX and LPA contribute to airway inflammation and hyperreactivity in asthma. Interestingly, recent early-phase clinical studies have demonstrated proof of concept that blocking ATX or LPAR1 might preserve lung function in patients with pulmonary fibrosis (25, 26). However, safety signals emerged during these studies (e.g. hepatotoxicity), which will hamper further development of these compounds. It should be possible to develop inhaled ATX or LPA antagonists that block LPA generation and/or signaling locally in the respiratory tract. If so, this strategy holds promise as a novel approach to minimize side effects and maximize therapeutic efficacy in asthma. In future studies, it will be important to identify biomarkers of ATX and LPA activity to monitor target engagement and identify better responding subgroups.

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