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Lipoxin A₄: a new direction in asthma therapy?

Expert Rev. Clin. Immunol. 9(6), 491–493 (2013)



Cindy Barnig

Department of Chest Disease, University Hospital of Strasbourg, 1 Place de l'Hôpital, Strasbourg 67091, France



Bruce D Levy

Author for correspondence: Pulmonary and Critical Care Medicine, Brigham & Women's Hospital, Boston, MA 02115, USA
Tel.: +1 617 525 5407
Fax: +1 617 525 5413
blevy@partners.org

“Cell-specific effects of lipoxin A₄ ... suggest that lipoxin A₄ can orchestrate the control of both early and late asthmatic inflammation and airway responses.”

Asthma continues to be a common and significant disease with substantial medical and economic unmet needs despite current therapies. In view of this medical and social imperative, the pathobiology of asthma is an area of active research in both academic and industrial laboratories. Perhaps most notably, 5–10% of individuals with asthma experience severe asthma that is refractory to current medical treatment [1]. In addition, there are no therapies available to actively resolve the uncontrolled immune responses in asthma.

Most individuals with asthma have airway inflammation that never completely resolves. The nature and extent of this inflammation varies by individual and by disease severity. In most cases, eosinophils and activated T cells accumulate in the lung. Th2 lymphocytes and eosinophils are increased in blood, lung tissue and bone marrow in most asthma clinical phenotypes. Many other cell types are implicated in the pathobiology of asthma and are likely to play prominent roles. Along these lines, many important functional responses have been assigned to mast cells, neutrophils and dendritic cells, as well as epithelial and mesenchymal cells [2]. These cells release inflammatory mediators, including Th2-associated cytokines, chemokines, growth factors and lipid mediators that drive the inflammatory process. In some individuals, changes in the airway epithelium, basement membrane and smooth muscle remodel the airway, potentially

leading to a component of fixed airflow obstruction.

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Innate lymphoid cells (ILCs) comprise a newly described family of hematopoietic effectors that serve protective roles in: innate immune responses to infectious microorganisms, lymphoid tissue formation, tissue remodeling after damage inflicted by injury or infection and the homeostasis of tissue stromal cells [3]. NK cells are prototypical members of the ILC family. Potential roles for NK cells in asthma and allergic disease have been recently defined in model systems, suggesting that NK cells can participate in the downregulation of allergic airway responses, including clearance of eosinophils and antigen-specific T cells [4]. In addition to NK cells, new ILC populations have been described, including a subset that can produce the Th2 cell-associated cytokines IL-5 and IL-13 in an antigen-independent manner. These cells are referred to as type 2 ILCs (ILC2s). They are involved in responses to helminth infection and murine models of allergic asthma and can respond to the epithelial-derived cytokines IL-25 (also known as IL-17E), IL-33 and thymic stromal lymphopoietin [5,6]. In addition, human ILC2s express the chemoattractant

receptor-homologous molecule expressed on Th2 cells CCR4, also known as prostaglandin D₂ receptor 2 [7]. We have recently shown that ILCs are present in human lungs in close proximity to mast cells and airway epithelial cells and that ILC2s generate IL-13 in response to the mast cell product prostaglandin D₂, principally through prostaglandin D₂ receptor 2 activation, and in a synergistic manner with the airway epithelial cytokines IL-25 and IL-33 [8]. Given the potency of IL-5 and IL-13 to initiate asthmatic immune responses in model systems, human ILC2s are likely to play important roles in allergen-independent inflammation in asthma.

Natural resolution of inflammation is an active host response. While it is driven, in part, by decrements in proinflammatory mediators [9], the promotion of resolution is now recognized as an active process with early signaling pathways engaging biosynthetic circuits for the later formation of counter-regulatory mediators [10]. Failure of acute inflammation to adequately resolve might contribute to the chronic airway inflammation in asthma pathobiology. Several classes of counter-regulatory lipid mediators have been recently discovered that are generated from essential fatty acids during inflammation to promote resolution [10]. Lipoxins (LXs) are the lead members of this new class of proresolving mediators.

The biological activity of the LXs in asthma and allergic disease has been defined over the past two decades. Bioactive, LXA₄ stable analogs have been prepared that in animal models block airway hyper-responsiveness and allergic inflammation, including eosinophil trafficking and tissue accumulation [11]. In humans, LXA₄ is generated during asthmatic responses [12] and, when administered to asthmatic subjects via nebulization, LXA₄ attenuates leukotriene C₄-induced bronchoconstriction [13]. In addition, treatment of allergic eczema in infants with topical 15(R/S)-methyl-LXA₄ decreases eczema severity and duration and improves patients' quality of life with similar efficacy to topical corticosteroids [14]. More severe variants of asthma, including aspirin-exacerbated respiratory disease, are associated with diminished LX biosynthesis compared with milder asthma [15–17], suggesting that the chronic inflammatory response in asthma may be due, in part, to defective generation of proresolving mediators leading to inadequate counter-regulation.

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LXs are enzyme-derived products of arachidonic acid metabolism. They are rapidly generated via biosynthetic circuits engaged during cell–cell interactions at sites of inflammation, act locally and then are rapidly inactivated by metabolic enzymes via pathways shared with other eicosanoids. LXA₄ is an agonist for ALX/FPR2 receptors, which are expressed on both human airway epithelial cells and leukocytes and can be induced by specific inflammatory mediators [10]. LXs demonstrate cell type-specific actions *in vitro*, including inhibition of granulocyte activation and locomotion, promotion of monocyte-derived macrophage phagocytosis of apoptotic granulocytes, blockade of T lymphocyte cytokine release and epithelial proinflammatory cytokine

and chemokine release. More recently, we described new cell-specific biological actions of LXA₄ on ILCs that would decrease inflammation in asthma [8]. First, we observed that both NK cells and ILC2s express the proresolving receptors ALX/FPR2 and CMKLR1 and that NK cells from subjects with severe asthma have increased ALX/FPR2 expression. When NK cells were exposed to LXA₄, the cells displayed an increase in NK cell-mediated apoptosis of both eosinophils and neutrophils. In addition, LXA₄ prevented prostaglandin D₂-stimulated release of IL-13 from ILC2s. These properties of LXA₄ are consistent with potent anti-inflammatory (ILC2) and proresolving (NK cell) effects on ILCs and highlight new putative mechanisms for the pathogenesis of severe asthma that links earlier observations of defective LXA₄ generation in severe asthma to the increased eosinophilia and chronic airway inflammation that characterize the disease.

“Natural resolution of inflammation is an active host response.”

Cell-specific effects of LXA₄ on eosinophils, macrophages, NK cells and ILC2 suggest that LXA₄ can orchestrate the control of both early and late asthmatic inflammation and airway responses. These potentially beneficial properties of LXs in the airway and in view of defective LX generation in uncontrolled asthma raise the possibility that LXA₄ or LXA₄ stable analogs could be useful in asthma therapy. Most of the biological asthma therapies currently under development target proinflammatory cytokines that are important during the onset of the asthmatic inflammatory response [2]. Variable responses have been observed among patients, probably because of substantial differences among the types of inflammation in asthma clinical phenotypes. Developing therapies based on endogenous mediators that are anti-inflammatory and proresolving agonists would represent a new and distinct drug development strategy. Although the two published human clinical studies with LXs show intriguing therapeutic promise for asthma and allergic diseases, more clinical trials of LXA₄ or stable analogs are needed to determine the potential utility of promoting endogenous resolution mechanisms in the treatment of asthma patients. The recent development of new LX stable analogs that are topically and orally active should enable further investigation of LX regulation in asthma.

In conclusion, innate immunity can play an important role in regulating asthmatic inflammation and airway responses and ILCs, including NK cells and ILC2s, can serve as targets for the counter-regulatory and proresolving actions of LXA₄, which displays potential as a new therapeutic strategy in asthma.

Acknowledgements

The work has been funded in part by AI068084 (BD Levy), HL107166 (BD Levy), HL109172 (BD Levy) and Fonds de dotation 'Recherche en Santé Respiratoire' 2011 (C Barnig).

Financial & competing interests disclosure

BD Levy is a co-inventor on patents related to lipoxin A₄ and asthma that have been licensed by the Brigham and Women's Hospital for clinical

development, and receives a share of licensing income through Brigham and Women's Hospital. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest

in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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