Arachidonic Acid 15-Lipoxygenase: Effects of Its Expression, Metabolites, and Genetic and Epigenetic Variations on Airway Inflammation

Xu Xu, Jingyun Li, Yuan Zhang, Luo Zhang

1Department of Otolaryngology Head and Neck Surgery, Beijing TongRen Hospital, Capital Medical University, Beijing, China
2Beijing Key Laboratory of Nasal Diseases, Beijing Institute of Otolaryngology, Beijing, China
3Department of Allergy, Beijing TongRen Hospital, Capital Medical University, Beijing, China

ABSTRACT

Arachidonic acid 15-lipoxygenase (ALOX15) is an enzyme that can oxidize polyunsaturated fatty acids. ALOX15 is strongly expressed in airway epithelial cells, where it catalyzes the conversion of arachidonic acid to 15-hydroxyeicosatetraenoic acid (15-HETE) involved in various airway inflammatory diseases. Interleukin (IL)-4 and IL-13 induce ALOX15 expression by activating Jak2 and Tyk2 kinases as well as signal transducers and activators of transcription (STATs) 1/3/5/6. ALOX15 up-regulation and subsequent association with phosphatidylethanolamine-binding protein 1 (PEBP1) activate the mitogen-activated extracellular signal-regulated kinase (MEK)-extracellular signal-regulated kinase (ERK) pathway, thus inducing eosinophil-mediated airway inflammation. In addition, ALOX15 plays a significant role in promoting the migration of immune cells, such as immature dendritic cells, activated T cells, and mast cells, and airway remodeling, including goblet cell differentiation. Genome-wide association studies have revealed multiple ALOX15 variants and their significant correlation with the risk of developing airway diseases. The epigenetic modifications of the ALOX15 gene, such as DNA methylation and histone modifications, have been shown to closely relate with airway inflammation. This review summarizes the role of ALOX15 in different phenotypes of asthma, chronic obstructive pulmonary disease, chronic rhinosinusitis, aspirin-exacerbated respiratory disease, and nasal polyps, suggesting new treatment strategies for these airway inflammatory diseases with complex etiology and poor treatment response.

Keywords: Arachidonic acid; respiratory tract; inflammation; genetics; epigenomics

INTRODUCTION

There is a high incidence of worldwide airway inflammatory diseases seriously affecting the quality of life of patients. Recent epidemiological surveys of the Chinese population have shown that the prevalence rates of asthma, chronic rhinosinusitis (CRS), and chronic obstructive pulmonary disease (COPD) are 4.2%, 2.1%, and 8.87%, respectively. These airway diseases often co-exist in patients and share common molecular mechanisms, which should be focused on in order to develop effective treatment approaches. In this review, we systematically analyzed the role of arachidonic acid 15-lipoxygenase (ALOX15), including its
genetic variations and epigenetic modifications, in eosinophilic inflammation, immune cell migration, and airway remodeling, which are the key processes underlying the development of different phenotypes of asthma, COPD, CRS, and aspirin-exacerbated respiratory disease (AERD). The clinical significance of ALOX15 as a potential drug target was also evaluated.

ALOX15 OVERVIEW

Enzymatic activity
Polysaturated fatty acids (PUFAs) and their metabolites play a vital role in the growth and development of normal cells. Lipoxigenases (LOXs) are heme-free dioxygenases that can catalyze the peroxidation of PUFAs to corresponding hydroperoxy derivatives. The human genome contains 6 functional LOX genes (ALOX15, ALOX15B, ALOX12, ALOX12B, ALOX5, and ALOXE3), each encoding a different LOX enzyme. ALOX15 (also called 15-LOX) uses physiological substrates such as arachidonic acid (AA), docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), α-linolenic acid (ALA), γ-linolenic acid (GLA), and linoleic acid (LA), which exist either in a free form or are incorporated into phospholipids, glycerides, or cholesterol esters. AA, an ω-6 PUFA representing a major component of the cell membrane phospholipids and the metabolic precursor of eicosanoids, is converted by ALOX15 into 15-[S]-hydroperoxyeicosatetraenoic acid (15-[S]-HPETE) and 15-hydroxyeicosatetraenoic acid (15-HETE), further metabolized into various bioactive molecules. The reactions of ALOX15 with DHA, EPA, and other substrates also produce metabolites with diverse physiological activities involved in the development of various diseases.

Physiological functions
Normally, ALOX15 is expressed in the cells of the hematopoietic, endocrine, immune, and respiratory systems, where it has different physiological functions and plays an important role in maintaining body homeostasis. In the respiratory system, ALOX15 has a higher level of expression in airway epithelial cells, where it releases chemokines acting on immune cells such as eosinophils, and regulates mucus secretion. In human airway epithelial cells, ALOX15 participates in the production of exoins (EXs) that increase the permeability of endothelial cells in vitro: 15-[S]-HPETE produced by ALOX15 from AA is converted into EXA4, which is used by glutathione transferase PH1 to generate EXC4 being further converted into EXD4 and EXE4. During mucociliary differentiation of normal human tracheobronchial epithelial cells, ALOX15 is not expressed at the early stage, but is strongly up-regulated at the late stage in fully differentiated cells, where it metabolizes AA and LA into 15-HETE and 13-hydroxyoctadecadienoic acid (13-HODE), respectively. Higher levels of ALOX15 in the epithelium correlate with the activation of extracellular signal-regulated kinase (ERK). ALOX15-generated 15-HETE is conjugated to phosphatidyethanolamine (PE) and then form 15-HETE-PE; both ALOX15 and 15-HETE-PE act as signaling molecules interacting with phosphatidyethanolamine-binding protein 1 (PEBP1) to activate ERK, thus resulting in the induction of interleukin (IL)-4 receptor α (IL-4Rα) downstream pathways. Under homeostatic conditions, PEBP1, also known as Raf-1 kinase inhibitor, binds to Raf-1 and prevents its phosphorylation, thus inhibiting Raf-1-mediated mitogen-activated protein kinase (MAPK) signaling. Furthermore, ALOX15 expression is induced by IL-4 and IL-13 through activation of Jak2 and Tyk2 kinases as well as signal transducers and activators of transcription (STATs)-1/3/5/6. Thus, after induction with IL-4/IL-13, both ALOX15 and its product 15-HETE-PE cause competitive dissociation of Raf1 from PEBP1 to activate ERK, which enhances the expression of IL-4Rα signaling-dependent genes. Cumulatively, these data indicate that in
human airway epithelial cells, ALOX15 interacts with PEBP1 to sustain MAPK/ERK activation and enhance pro-inflammatory signaling pathways related to airway diseases.

ALOX15 type B (ALOX15B), first found by Brash et al. in the human skin, has about 40% homology with ALOX15 and shows similar enzymatic activity towards AA; it differs from ALOX15 in the catalytic profile as well as in tissue distribution. Thus, the expression of ALOX15 in human macrophages is inducible, whereas that of ALOX15B is constitutive, suggesting that ALOX15B is involved in the maintenance of lipid homeostasis in macrophages; however, its role in the respiratory system is not as significant as that of ALOX15.

ROLE OF ALOX15 IN AIRWAY INFLAMMATORY DISEASES

ALOX15 and its metabolites are important factors in the pathophysiology of diseases of both the lower respiratory tract (asthma and COPD) and the upper respiratory tract (CRS and AERD) because of their role in the regulation of eosinophil-mediated inflammation, migration of immune cells (immature dendritic cells, activated T cells, and mast cells), and airway remodeling including goblet cell differentiation. Here, we summarize the pathological effects of ALOX15 and its metabolites in various airway diseases (Table) as well as the molecular mechanisms underlying airway inflammation (Fig. 1).

ALOX15 promotes eosinophilic inflammation

Although ALOX15 is not expressed in unstimulated human peripheral macrophages, it is significantly up-regulated by type 2 inflammatory factors. In patients with asthma, airway macrophages are the main source of 15-HETE, whose level correlates with tissue eosinophil numbers, sub-basement membrane thickness, and expression of tissue inhibitor of metalloproteinase-1 in bronchoalveolar lavage fluid (BALF). Another ALOX15 product in macrophages, 12-[[S]-HETE, has been shown to cause bronchial epithelial damage in asthma.

In addition to macrophages, ALOX15 is strongly expressed in airway epithelial cells under physiological and pathological conditions. Ordovas-Montanes et al. carried out comprehensive expression profiling in CRS using single-cell RNA sequencing and revealed the difference in ALOX15 expression between non-polyp and polyp tissues. In non-polyp tissues, ALOX15 was found to be mainly expressed in ciliated cells, whereas in polyps, its expression was high in ciliated, apical, basal, and glandular cells.

Several studies have proved that ALOX15 participates in eosinophil-mediated inflammation, which plays a key role in the occurrence and progression of asthma and COPD.

Table. The involvement of ALOX15 and its metabolites in the pathogenesis of airway inflammatory diseases

| Disease | ALOX15 expression | Main metabolites | Pathogenesis | Reference |
|---------|-------------------|-----------------|--------------|-----------|
| Asthma  | Upregulated in bronchial epithelium and macrophages | 15-HETE, 15-HETE, 5,15-diHETE, 13-HODE, 12-[[S]-HETE, 15-HETE-PE | Tissue eosinophilic inflammation, Airway hyperresponsiveness, Bronchial epithelial damage, Goblet cell metaplasia and mucus hypersecretion | 23,24,31,25 |
| CRS     | Upregulated in nasal epithelium | 15-HETE, ND | Tissue eosinophilic inflammation, Epithelial-mesenchymal transition | 35,49 |
| COPD    | Upregulated in whole blood | ND | Tissue eosinophilic inflammation | 27 |
| AERD    | Upregulated in nasal epithelium | 15-HETE, 15-HETE-PE | Abnormal metabolism of AA | 37-39 |

AA, arachidonic acid; AERD, aspirin-exacerbated respiratory disease; ALOX15, arachidonic acid 15-lipoxygenase; COPD, chronic obstructive pulmonary disease; CRS, chronic rhinosinusitis; 5,15-diHETE, 5,15-dihydroxyeicosatetraenoic acid; ERK, extracellular signal-regulated kinase; 15-HETE, 15-hydroxyeicosatetraenoic acid; PE, phosphatidylethanolamine; 13-HODE, 13-hydroxyoctadecadienoic acid; 12-[[S]-HETE, 12-[[S]-hydroxyeicosatetraenoic acid; ND, not determined.
A proportion of patients with COPD (20%–40%) have eosinophilic inflammation and demonstrate the up-regulation of ALOX15 expression.27,28 Similarly, most patients with asthma have a pattern of allergic inflammation in the airways characterized by eosinophilia.29 In the BALF of patients with asthma, the level of 15-HETE, which is the main metabolite of the ALOX15 pathway, is significantly higher than in that of normal individuals, and highest in patients having severe asthma with airway eosinophilia.30 Transcriptome analysis of blood samples from 298 patients with moderate to severe asthma revealed that ALOX15 was one of the 50 genes showing the strongest correlation with the absolute eosinophil count in peripheral blood, and that its expression could predict eosinophilic airway inflammation, blood eosinophil numbers, and anti-IL-13 therapeutic effect.30 In patients with asthma treated with benralizumab, a humanized non-glycosyl monoclonal antibody targeting the
IL-5 receptor, ALOX15 expression was significantly decreased, and this effect was stronger in patients with high eosinophil counts than with low eosinophil counts. In a mouse model of asthma induced by house dust mites, the levels of various ALOX15 products, such as 15-HETE, 5,15-dihydroxyeicosatetraenoic acid (5,15-diHETE), and 13-HODE were significantly increased, resulting in airway hyperresponsiveness and pulmonary eosinophilia. Overall, these findings indicate that ALOX15 and its metabolites stimulate eosinophilia in airway diseases, thus playing a key role in subsequent airway inflammation.

In addition to lower respiratory tract diseases, ALOX15 has a similar pro-inflammatory function in upper respiratory tract diseases including CRS and AERD. CRS is a complex heterogeneous condition usually characterized by type 2 inflammation driven by IL-5 and IL-13, which activate inflammatory cells such as mast cells and eosinophils. It has been shown that ALOX15 expression is significantly increased in all patients with CRS compared to healthy controls. A recent study has indicated that the expression of ALOX15 is significantly up-regulated in nasal polyp (NP) epithelial cells and middle turbinate epithelial cells of patients with chronic rhinosinusitis with nasal polyps (CRSwNP) and co-localized with that of eosinophil chemokine ligand 26 (CCL26), which mediates the recruitment and activation of eosinophils at inflammation sites. In addition, increasing evidence suggests that ALOX15-produced 15-HETE plays an important role in aspirin intolerance. Furthermore, ALOX15 expression and 15-HETE production have been shown to be increased in patients with CRS and aspirin intolerance.

Altogether these data indicate that ALOX15 participates in the airway diseases of the upper and lower respiratory tracts by regulating eosinophilic inflammation. In airway epithelial cells of patients with asthma or CRSwNP, IL-4 and/or IL-13 not only induce ALOX15 expression and 15-HETE-PE production, but also up-regulate CCL26 through activation of the MAPK/ERK pathway. In turn, CCL26 activates C-C chemokine receptor 3 (CCR3), thus stimulating the infiltration of eosinophils from the circulation into tissues, which is closely related to the pathogenesis of airway inflammatory diseases.

**ALOX15 promotes the migration of immune cells**

The increased infiltration of immature dendritic cells, activated T cells, and mast cells into airway tissues is an important feature of airway inflammatory diseases such as asthma and COPD. In an A549 cell model, Liu et al. found that the ectopic expression of ALOX15 resulted in the production of 15-HETE, 8S,15S-diHETE, and 15-keto-6Z,8Z,11Z,13E-eicosatetraenoic acid (15-KETE), as well as the secretion of chemokines macrophage inflammatory protein (MIP)-1α (CCL3), MIP-1β (CCL4), RANTES (CCL5), and IP-10 (CXCL10), which promoted the migration of immature dendritic cells, activated T cells, and mast cells in the chemotaxis experiment. Antibody neutralization experiments have shown that the enhanced immune cell recruitment mainly depends on the up-regulation of RANTES and MIP-1 release induced by ALOX15. The siRNA-mediated knockdown of ALOX15 leads to reduced levels of 15-HETE and the down-regulation of MIP-1α, RANTES, and IP-10. These results indicate that ALOX15 overexpression in human airway epithelial cells can cause transcriptional activation of chemokines-encoding genes, which results in the enhanced migration of immune cells to inflammatory sites. Although the underlying mechanism is still unclear, it could play an important role in the occurrence and progression of airway inflammatory diseases.

**ALOX15 promotes airway remodeling**

Airway remodeling is an important process in the pathogenesis of airway diseases. Studies in models of human asthma have shown that ALOX15 and its main product, 15-HETE-PE,
are essential for pulmonary tissue remodeling, especially for the differentiation of goblet cells. Thus, it has been shown that in airway epithelial cells, IL-13 not only induces ALOX15 expression and production of 15-HETE-PE which increases the synthesis of mucin 5AC (MUC5AC), but also up-regulates the expression of periostin, a protein that promotes the migration and adhesion of eosinophils, and promotes subepithelial fibrosis. At the same time, IL-13-induced ALOX15 expression correlates with the up-regulation of FOXA3 and downregulation of FOXA2. FOXA3, a transcription factor binding to proximal promoters of genes associated with goblet cell metaplasia, was reported to induce goblet cell metaplasia and enhance MUC5AC expression, whereas FOXA2, another transcription factor functioning in airway epithelial cells, reduced goblet cell metaplasia and stimulated ciliated cell differentiation. The knockout of ALOX15 by siRNA significantly down-regulated the expression of FOXA3, MUC5AC, and periostin induced by IL-13, whereas exogenous 15-HETE-PE could up-regulate these factors even in the absence of IL-13 stimulation. These data further prove that 15-HETE-PE generated by ALOX15 participates in airway tissue remodeling in asthma by stimulating goblet cell differentiation and periostin expression. Although the mechanisms by which ALOX15 controls the expression of FOXA transcription factors need further investigation, it is possible that ERK/MAPK activation and/or the interaction of membrane phospholipids with IL-4Rα or its downstream signaling pathways may be involved.

In addition, it has been shown that in CRSwNP infiltrated by eosinophils, the basement membrane thickness was larger, and that the matrix metalloproteinase 1 expression positively correlates with ALOX15 transcription.

Thus, ALOX15 plays an important pathophysiological role in airway tissue remodeling associated with airway inflammation, suggesting that it is a critical factor in the natural course of airway diseases.

**GENETIC VARIATIONS AND EPIGENETIC MODIFICATIONS IN ALOX15**

The presence of multiple variants of the ALOX15 gene and its epigenetic modifications, including DNA methylation and histone modification, are related to a variety of airway diseases (Fig. 2).

**Genetic variations**
Numerous studies indicate that there are several mutations at various positions of the ALOX15 gene, which have different effects on airway diseases, increasing or decreasing the risk of disease development. Therefore, the assessment of the allele frequency of these ALOX15 variants in the population and their pathophysiological role is essential for the development of effective treatment strategies.

Wittwer et al. detected the c.-292C>T mutation in the ALOX15 promoter region, which doubled ALOX15 transcription in macrophages, suggesting that the presence of this ALOX15 variant may increase the production of AA metabolites participating in the pathogenesis of asthma. Some ALOX15 variants have been shown to exacerbate inflammation by regulating the synthesis and release of pro-inflammatory IL-6. Thus, Fairfax et al. reported that specific ALOX15 polymorphisms (rs11078527 and rs11568131) were significantly associated with IL-6 production in lipopolysaccharide-stimulated primary human peripheral blood mononuclear
cells and could influence the expression of tumor necrosis factor (TNF) and IL-1β through trans-acting effects, thereby promoting acute inflammation.

While some ALOX15 variants are pro-inflammatory and may increase the susceptibility to airway inflammatory diseases, others have been found to reduce the risk of airway inflammation. Tremblay et al.\textsuperscript{52} reported the protective effects of ALOX15 variants rs2664593 and rs7217186 in allergic asthma and airway hyperresponsiveness. Ferreira et al.\textsuperscript{53} conducted a genome-wide association study (GWAS) on a wide range of allergic disease phenotypes in 180,129 patients with asthma, hay fever, and/or eczema in Europe and detected 136 independent risk-associated variants; among them, ALOX15 rs71368508 could reduce the risk of allergic diseases. Another ALOX15 variant has been suggested to have a significant protective effect against developing NPs and CRS. Kristjansson et al.\textsuperscript{54} in a GWAS study with 4,366 NP and 5,608 CRS samples from Iceland and the UK revealed gene mutations related to NPs and CRS; among them, the highest association with the diseases was shown by low-frequency ALOX15 missense variant rs34210653 (p.T560M), which could reduce the risk of NPs and CRS by 68% and 36%, respectively. Schurmann et al.\textsuperscript{55} showed that the p.T560M ALOX1 mutant lacked an OH group and could not form a hydrogen bridge, which significantly reduced its catalytic activity. This finding suggests that the p.T560M substitution in ALOX1 may decrease the production of pro-inflammatory mediators in eosinophils and nasal mucosal epithelial cells as well as reduce the number of circulating eosinophils, thus protecting against NPs and CRS. It is worth noting that the frequency of rs34210653 (p.T560M) varies among racial groups: it is highest in Hispanics (8.0%), followed by white Europeans (1.2%), lowest in Black/African Americans (0.5%), and not detected in East Asians (0%),\textsuperscript{56} suggesting that the association of rs34210653 with CRS and NPs may be race-specific.

**Epigenetic modifications**

Several studies have indicated that epigenetic mechanisms regulate the transcription of the ALOX15 gene in the airway epithelium and that methylation and acetylation modifications are increased in inflammation. Thus, a recent study of children with allergic asthma found...
significant changes in the methylation status of 47 allergy-associated genes involved in asthma, which inversely correlated with gene expression: in particular, the hypomethylation of ALOX15 increased its expression, which was associated with the pathogenesis of asthma. Besides DNA methylation, histone modifications at the ALOX15 promoter site also play a key role in transcriptional regulation. There is evidence that in IL-4-treated epithelial cells, the hypomethylation in histone H3 trimethyllysine 27 (H3K27me3) at the ALOX15 promoter upregulates ALOX15 expression. It was found that in colon cancer cells, the acetylation of H3 and H4, and hypomethylation at the H3K9 site could activate ALOX15. However, further studies are needed to confirm the role of histone modifications in airway diseases. These results characterize ALOX15 as an epigenetic marker for airway diseases because DNA hypomethylation and histone modifications up-regulating ALOX15 expression should result in the elevated production of pro-inflammatory metabolites involved in all stages of airway inflammation-related diseases.

**EFFECTS OF ALOX15 INHIBITORS**

Several natural compounds, such as flavonoids, coumarins, catechins, and emodin, have been shown to exert significant inhibitory effects on ALOX15. These inhibitors act on distinct regulatory pathways and may potentially have therapeutic effects on airway inflammation. Flavonoids are powerful antioxidants with anti-allergic activity, which can suppress the release of pro-inflammatory mediators and Th2 cytokines (IL-4 and IL-13), and down-regulate CD40 ligand expression in high-affinity immunoglobulin E (IgE) receptor-positive cells (mast cells and basophils), thus making flavonoid intake beneficial for patients with asthma. Coumarin derivatives can reduce allergic inflammation by reducing the release of histamine and the secretion of TNF-α, IL-1β, and IL-4. Epigallo-catechin-3-gallate is a catechin that can inhibit the epithelial-mesenchymal transition induced by transforming growth factor β1 (TGF-β1) and prevent the migration of human bronchial epithelial cells, thereby reducing airway remodeling in asthma. In a mouse model of asthma, emodin was found to suppress the infiltration of inflammatory cells through inhibition of the Notch pathway and decrease the levels of inflammatory cytokines such as IL-5, IL-17, and interferon-γ in BALF and serum. These data indicate that plant-derived ALOX15 inhibitors have therapeutic potential in the treatment of airway inflammatory diseases.

**CONCLUSIONS**

The role of ALOX15 in airway diseases is underlain by its regulation of eosinophil-mediated inflammation through the ALOX15-15-HETE-PE axis, which activates ERK and the downstream IL-4Rα signaling pathway controlling eosinophil trafficking to the sites of allergic inflammation. However, it should be noted that the targets of the metabolites produced by ALOX15 as well as the mechanisms regulating the expression of pro-inflammatory chemokines and airway remodeling-related transcription factors are still unclear. Therefore, future studies are needed to determine whether, in addition to the ERK pathway, other signaling mechanisms are regulated by ALOX15. Although GWAS studies on ALOX15 have revealed exciting data, they have mainly been conducted on the European population, and it is unclear whether the effects of the identified ALOX15 variants on airway diseases are race-specific; therefore, further research is needed to determine the clinical significance of ALOX15 mutations in different racial groups. Limited pharmacological
agents targeting the ALOX15 pathway have been approved for use so far. However, previously discovered protective loss-of-function variants such as proprotein convertase subtilisin/kexin type 9 (PCSK9) have been successfully used in clinical practice and have guided further drug development studies. Leukotriene inhibitors are a class of drugs that act by inhibiting the action of 5-lipoxygenase (5-LOX), a member of the lipoxygenase family highly similar to ALOX15, which was approved for use in asthma and allergic rhinitis. These data show that the compounds targeting ALOX15 present a new strategy for the treatment of allergic diseases, providing a foundation for the development of novel anti-allergy drugs, taking into consideration the genomic data. Furthermore, the findings of Forno et al. support the feasibility of using the nasal methylome for future clinical applications, such as predicting the development of asthma among wheezing infants. The epigenetic modifications of ALOX15, which may serve as markers in the diagnosis and risk prediction of airway inflammatory diseases, should be further investigated. The development and testing of ALOX15-targeting drugs for therapeutic intervention in airway inflammatory diseases is the focus of our future work. Extensive studies on the genetic and epigenetic mechanisms would yield valuable information about the clinical potential and enhance our understanding of the etiology of airway inflammatory diseases.

ACKNOWLEDGMENTS

This work was supported by grants to the national key R&D program of China (2016YFC20160905200), the program for the Changjiang scholars and innovative research team (IRT13082), the national natural science foundation of China (81630023, 81970849 and 82071022), Beijing municipal science and technology project (Z181100001618002), CAMS Innovation Fund for Medical Sciences (2019-I2M-5-022), Beijing Municipal Administration of Hospitals’ Mission Plan (SML20150203), Beijing health bureau program for high level talents (2014-3-018), Cross-disciplinary Collaborative Program of Beijing Nova Program (xjc201712), and public welfare development and reform pilot project (2019-10).

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