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Resolution of Inflammation in Asthma

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Synopsis

The resolution of inflammation in healthy airways is an active process with specialized mediators and cellular mechanisms that are enlisted to restore tissue homeostasis. In this article, we will focus on recent discoveries of natural mediators derived from essential fatty acids, including omega-3 fatty acids, that have anti-inflammatory and pro-resolving actions. These specialized pro-resolving mediators serve as agonists at specific receptors. Asthma is a disease of chronic, non-resolving inflammation of the airway without known cure. While the biosynthesis of pro-resolving mediators occurs during asthma, defects in their production are associated with disease severity, suggesting that the pathobiology of asthma may result from impaired resolution of airway inflammation.

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Keywords

inflammation; resolution; lipoxins; mediators; asthma

Introduction

Asthma is characterized by increased and chronic airway inflammation³⁹. Airway sampling by bronchoscopy or sputum analysis most often reveals abundant eosinophils and activated T cells and lung histology demonstrates airway remodeling with disordered mucosal epithelium^{21,24}. While noxious stimuli, including potential allergens, can initiate an acute inflammatory response that is self-limited, non-resolving inflammation is linked to asthma and other chronic inflammatory diseases (reviewed in ⁷³). The overall magnitude and duration of inflammation depends on competing physiological processes, namely pro-inflammatory mechanisms that amplify inflammation and endogenous braking programs that control the resolution of inflammation (reviewed in ⁹²). In health, the resolution of inflammation is an active coordinated process that is spatiotemporally controlled by endogenously generated autacoids at sites of inflammation⁶². While several classes of mediators participate in resolution, the enzymatic transformations of polyunsaturated fatty acids (PUFAs) to specific pro-resolving agonists are of particular interest. The discovery that PUFAs are essential dietary constituents ²³ led to the recognition of their immunoregulatory actions⁹¹. These PUFA-derived mediators display cell-type selective anti-inflammatory, pro-resolving, anti-fibrotic, anti-angiogenic and anti-infective actions (reviewed in ⁹²).

Here, we review recent findings on new mechanisms and mediators for resolution of airway inflammation with a focus on their relevance to asthma.

Resolution of acute inflammation

The acute inflammatory response to inhaled pathogens, particles and toxins is inherently protective and essential to ultimately restoring the injured airway to its normal physiological functioning. Acute inflammation is initiated within minutes of recognition of a danger signal, and is generally self-limited, resolving within hours or days. In several conditions that are clinically recognized as lung disease, including asthma, chronic inflammation persists. Somehow, a naturally protective response becomes unrestrained and leads to chronic changes to airway structure and function. In most individuals with asthma, it is this chronic inflammation that causes the clinical expression of symptoms, namely cough, mucus, chest tightness, wheeze and shortness of breath. There is a rapidly expanding exploration of the natural mechanisms and mediators of resolution that limit acute inflammation in healthy tissues and this information has turned conventional thinking on its head regarding the pathophysiology of asthma and other chronic inflammatory diseases.

Resolution is now appreciated to be an active process that terminates acute inflammation ^{62,95,101}. At present, we know that efficient restoration of inflamed tissues to their basal state requires that inflammatory cells are effectively cleared and further neutrophil recruitment is abrogated. During this process, tissue neutrophils undergo apoptosis and are recognized and subsequently engulfed by phagocytic macrophages in a non-inflammatory manner ^{85,87}. Clearance of apoptotic neutrophils also leads to the production of additional mediators that suppress the progression of inflammation and promote repair of damaged tissues ^{38,42,86}. Dysregulation of this process leads to unresolved inflammation, which underlies the pathology of several chronic inflammatory disease processes^{45,92}. Hence, resolution of inflammation requires cellular interactions in the

affected tissues in order to re-establish a homeostatic state after a limited period of inflammation. This sequence of events is also referred to as 'catabasis' - the reversion from a pathological to a non-inflammatory state of tissue homeostasis^{12,103}.

In health, the acute inflammatory response is self-limited. Early tissue edema (minutes-hours) and neutrophil accumulation (hours to days) will decrease with time and lymphocytes, macrophages and other monocytoïd cells will traffic to the inflamed tissue to restore homeostasis⁶⁸. While anti-leukocyte actions are commonly considered anti-inflammatory, it is important to view each cell types' roles in this dynamic process of inflammation resolution (aka catabasis). Inhibition of neutrophil transmigration and activation is anti-inflammatory while restitution of barrier integrity (endothelial, epithelial or both), recruitment of monocytoïd cells, and promotion of macrophage clearance of apoptotic cells, microbes and tissue debris are all pro-resolving. In the lung, restitution of barrier integrity is of heightened importance secondary to concern for alveolar edema leading to hypoxemia. Thus, lung specific pro-resolving events include clearance of edema and transitional matrix, repopulation of the airway epithelia and restoration of pulmonary surfactants.

For resolution of adaptive immune responses, allergen-specific or pathogen-specific effector T cells and inflammatory macrophages need to be cleared from the lung. Direct and indirect mechanisms for T cell clearance include Natural Killer (NK) cell direct cytotoxicity, macrophage engulfment of apoptotic T cells and decrements in pro-inflammatory mediators.

The majority of individuals with asthma have chronic inflammation of the airways that does not resolve. Perhaps as many as 50% of adult asthmatics and an even higher proportion of pediatric asthmatic individuals have an expansion of allergy airway inflammation that is characterized by an abundance of CD4+ TH2 cells with increased interleukin (IL)-5 and IL-13 production^{116,117}. IL-5 is a potent chemoattractant and activator of eosinophils, which are also present in large numbers in most asthmatic subjects³⁹. Eosinophils and mast cells release significant amounts of the cysteinyl leukotrienes (CysLTs; LTC₄, LTD₄ and LTE₄) and LTD₄ is the most potent constrictor of airway smooth muscle identified to date⁸². These mediators also induce vascular permeability changes and tissue edema. IL-13 leads to mucous metaplasia of the bronchial epithelium with increased airway mucus^{114,121}. Together, the increased numbers of airway leukocytes (T cells, eosinophils), pro-inflammatory (IL-5, IL-13) and pro-phlogistic (CysLTs) mediators, smooth muscle constriction and mucus production by epithelial cells lead to airway narrowing and hyperactivity.

While chronic eosinophilic bronchitis is common in asthma, the condition is syndromic and airway pathobiology is more complex in many individuals with asthma. Some experience a predominately neutrophilic infiltration, and others are pauci-immune, likely reflecting a primary disorder of airway smooth muscle⁷². Environmental factors, such as cigarette smoke, microbial pathogens and air pollution, can lead to mixed and more complex airway inflammation³⁹. Despite the presence of airway inflammation in the vast majority of individuals with asthma, there is still limited understanding of why the asthmatic airway inflammation fails to resolve. In addition, potent anti-inflammatory agents such as glucocorticoids are available, yet their use does not cure asthma. Once adults are diagnosed with asthma, this is most often a life-long illness. Thus, important questions remain to be answered in determining why asthmatic inflammation fails to resolve, so that pro-resolving therapeutics can be developed.

Anti-inflammation and pro-resolution are distinct physiological processes⁹³. The identification of pro-resolving mediators that facilitate the clearance of inflammatory cells

and debris from inflamed tissue has improved our understanding of the distinction between pro-resolving and purely anti-inflammatory mediators (reviewed in ⁹²). While anti-inflammatory mediators block granulocyte tissue entry and activation, endogenous pro-resolving mediators accelerate the restitution of tissue homeostasis and clearance of inflammatory cells without concomitant immunosuppression. To this end, pro-resolving mediators decrease allergic edema¹¹, recruit monocytes in a non-phlogistic fashion⁶⁷, increase phagocytosis and efferocytosis by macrophages⁴⁶, increase chemokine scavenging by apoptotic neutrophils (via CCR5 expression)⁵, enhance luminal clearance of tissue neutrophils by CD55 expression⁵⁹ and augment mucosal host defense via expression of anti-microbial proteins^{25,26}. These pro-resolution mediators can also stimulate the secretion of transforming growth factor (TGF)- β 1 and IL-10 that can also dampen inflammation^{12,107}.

For asthma, currently available anti-inflammatory agents [*e.g.*, glucocorticoids (GCs) and the biological therapeutics anti-IgE, IL-5 or IL-13] target pro-inflammatory mediator pathways³⁹. In addition, asthmatic individuals may use non-steroidal anti-inflammatory drugs that inhibit cyclooxygenases (COX) and zileuton that inhibits 5-lipoxygenase (ALOX5). These agents can interfere with inflammation resolution, because these enzymes are also involved in the endogenous formation of pro-resolving mediators^{43,44,89}. Thus, new disease-modifying therapeutic agents are needed that are specifically designed to prevent further inflammation and promote resolution.

Polyunsaturated fatty acid metabolism to pro-resolving mediators

Polyunsaturated fatty acids (PUFAs) are essential nutrients. The ω -6 PUFA, arachidonic acid (AA; 20:4 n -6) is incorporated into cellular phospholipids, and upon cell activation, specific phospholipase A₂ enzymes release AA from the *sn*-2 fatty acyl bond of phospholipids. AA can then be converted enzymatically by COX to prostaglandins (PGs), by ALOX5 to leukotrienes (LTs) or, by ALOX5 in collaboration with ALOX12 or ALOX15 to lipoxins (LXs)^{83,92}. The ω -3 PUFAs eicosapentaenoic acid (EPA; 20:5 n -3) and docosahexaenoic acid (DHA; 22:6 n -3) are enriched in neural and mucosal tissues^{14,40}. In whole blood from healthy subjects, the total fatty acid pool contains both EPA (~0.5 to 2.8% of total fatty acids) and DHA (~1.3 to 5.0%)^{1,47,57,71,74,113}. These ω -3 PUFAs are also available at sites of inflammation for enzymatic transformation to resolvins, protectins, maresins and other new families of pro-resolving mediators^{95,98,101,104,119}. These new specialized mediators display receptor-mediated cell type specific actions (Table 1). Because information on these mediators in airway health and asthma is, at this point, limited, we will focus in this review on lipoxin A₄ (LXA₄), the E-series resolvins termed resolvin E1 (RvE1) and protectin D1 (PD1) and highlight their formation, sites of action and potential anti-inflammatory and pro-resolving actions with particular reference to available information on allergic airway inflammation and asthma.

Lipoxin A₄

Lipoxins (LXs) are tri-hydroxy tetraene containing mediators derived from the sequential actions of LOXs (reviewed in ⁹²). Because LX biosynthetic enzymes (*i.e.*, LOXs) are predominately compartmentalized in distinct cell types, LXs are principally generated during heterotypic cell-cell interactions in multicellular host responses, such as inflammation. LXs are structurally and functionally distinct from PGs and LTs. Tissue levels of these pro-phlogistic eicosanoids (PGs and LTs) are prominent during the onset of inflammation while LXs are increased during resolution. LXs have cell type specific actions (Table 1), including inhibition of neutrophil (PMN) and eosinophil trans-endothelial and trans-epithelial migration, and PMN reactive oxygen species generation, and stimulation of monocyte chemotaxis and macrophage engulfment of apoptotic PMNs. LXs also display

neuro-modulatory actions at capsaicin-sensitive sensory nerves in the guinea pig⁷⁰ and can dampen inflammatory pain processing in mice¹¹⁰. In the lung, ALOX15 is a key enzyme for LX generation and is expressed by many cells in the inflamed lung, including bronchial epithelial cells, macrophages and eosinophils^{54,66,100,105}. ALOX15 converts C20:4 to 15(S)-hydroperoxyeicosatetraenoic acid (15(S)-H(p)ETE) that can be further converted to LXs by ALOX5⁶⁶. Thus, LX biosynthesis can occur when infiltrating PMNs or eosinophils interact with epithelia in inflamed airways^{62,63}. LXs can also be generated in the vasculature during collaborations between leukocyte ALOX5 and platelet ALOX12. Human platelet ALOX12 is a LX synthase that can generate LXs from ALOX5 derived leukotriene A₄ (LTA₄).

LX epimers are also generated during inflammation and can be increased in the presence of aspirin (acetylsalicylic acid (ASA))³³. Acetylation of COX-2 by ASA blocks prostaglandin synthesis; however, the enzyme remains catalytically active, converting AA to 15(R)-hydroxyeicosapentaenoic acid (15(R)-HETE) rather than PG. 15(R)-HETE can serve as a substrate for leukocyte ALOX5 for subsequent transformation to 15-epimer-LXs³³. 15(R)-HETE can also be generated by cytochrome P450 metabolism of C20:4 in epithelial cells³². Of interest, statins can also increase 15-epimer-LX production¹⁷, including in the airway⁷⁹.

At sites of inflammation, LXs are rapidly formed and rapidly inactivated. The enzyme 15-hydroxyprostaglandin dehydrogenase (15-PGDH) metabolizes LXs by dehydration to convert LXA₄ into 15-oxo-LXA₄⁹⁶. This conversion inactivates the LXs, as the oxo-LXs no longer display counter-regulatory bioactions. 15-oxo-LXA₄ can be further metabolized by eicosanoid oxidoreductase, which specifically reduces the double bond adjacent to the ketone, and then again by 15-PGDH to a 13,14-dihydro-LXA₄. LX metabolism is stereo-specific, so 15-epi-LXs are metabolized less efficiently than LXs, increasing their biological half-life approximately 2-fold and thereby enhancing their ability to evoke bioactions¹⁰². Thus, ASA's unique pharmacological properties arise from both its ability to inhibit pro-inflammatory PG formation and its capacity to generate anti-inflammatory lipid mediators, including the 15-epi-LXs¹⁰⁹. This biosynthetic paradigm for ASA-triggered counter-regulatory lipid mediators from AA is also observed for the ω -3 polyunsaturated fatty acids C20:5 (eicosapentaenoic acid) and C22:6 (docosahexaenoic acid)¹⁰⁹.

Lipoxin A₄ receptors

LXA₄ is an agonist, interacting with specific receptors (termed ALX/FPR2). ALX/FPR2 receptors are 7-transmembrane, G-protein coupled receptors that are expressed on several cell types, including human PMNs, eosinophils, monocytes/macrophages, enterocytes, synovial fibroblasts and airway epithelium³⁰. LXs bind to ALX/FPR2 with high affinity (K_d= 1.7nM)²⁹. Asthma biologists will recognize that the DP2 receptor can bind both peptide and lipid ligands⁵², but ALX/FPR2 was the first receptor described with these properties⁹⁷. This dual recognition of structurally distinct ligands is now appreciated to be a more generalized phenomenon^{30,7}. In PMNs, ALX/FPR2 transduces stop signals in part via polyisoprenyl phosphate remodeling⁶⁴ and inhibition of leukocyte specific protein (LSP-1) phosphorylation, a downstream regulator of the p38-MAPK cascade⁷⁵.

Cytokines, including IL-13 and IFN- γ , can induce ALX/FPR2 expression in airway epithelial cells and enterocytes⁴⁸ and the ALX/FPR2 promoter was recently characterized¹⁰⁶. Lung ALX/FPR2 expression is also induced *in vivo* in a murine model of allergic airway inflammation⁶³. Transgenic mice that express human ALX/FPR2 receptors have demonstrated the importance of these receptors in regulating experimental inflammation³⁷, including allergic airway responses⁶³.

In addition to ALX/FPR2, additional receptors have been identified for LXA₄, including the intracellular aryl hydrocarbon receptor (AhR)⁸⁸ and CysLT1 receptor^{9,49}. LX signaling via AhR can attenuate IL-12 release from dendritic cells². LXA₄ interaction with CysLT1 receptors antagonizes CysLT binding⁴⁹. Together, these findings indicate that LXs can serve as agonists (via ALX and AhR) to transduce cell type specific anti-inflammatory and pro-resolving actions and as antagonists (at CysLT1) to block pro-phlogistic signaling.

Lipoxin A₄ in allergic airway responses and asthma

Lipoxins are present in BALFs and sputum in asthma^{60,78,112}. Because LXs can block LTD₄-mediated constriction of isolated lung strips *in vitro*,³⁶ LXA₄ was given via nebulizer to asthmatic subjects prior to airway provocation challenges with inhaled LTC₄, and LXA₄ displayed protective actions in human asthmatic airways³¹.

Translational research has uncovered a decreased ability to generate LXs in aspirin-exacerbated respiratory disease⁸⁴ and other forms of severe asthma^{61,78} (Table 2). Relative to milder asthma, blood from severe asthmatics has a reduced capacity to convert AA to ALOX15 catalyzed products, including 15-HETE and LXA₄^{28,61}, and levels of LXA₄ in bronchoalveolar lavage fluids (BALFs) are markedly decreased in severe compared to non-severe asthma⁷⁸. LXA₄ levels are also lower in supernatants of induced sputum in severe compared to mild asthma¹¹². In addition, lower levels of LXA₄ are associated with exercise-induced asthma¹¹¹. Decreased formation of LXs in uncontrolled asthma has now been identified in culturally distinct populations of adults and children from several countries, including the U.S., Poland, France, Turkey and China (Table 2). Decreased LX generation in uncontrolled asthma is partially explained by dysregulated expression of LX biosynthetic genes that vary by both disease severity and anatomic compartment⁷⁸. In contrast, generation of the ALOX5 derived products 5-HETE, LTB₄ and CysLTs are all increased in asthma, in particular severe asthma⁶¹. Peripheral blood LXA₄ and the individualized ratio of LXA₄/CysLTs correlate with lung function (FEV1 percent predicted values)^{28,61}, suggesting a link between AA metabolism to these bioactive lipids and airflow obstruction in asthma. Lower LX levels have also been described in the airways of patients suffering from cystic fibrosis and interstitial lung disease and appear to play important roles in the pathobiology of these inflammatory lung diseases as well^{55,58}. Together, these results indicate that LXs are generated during airway inflammation and decrements in their generation can contribute to the pathogenesis of asthma.

Novel Omega-3 fatty acid derived lipid mediators

Population surveys report that diets rich in omega-3 fatty acids are associated with lower asthma prevalence⁹⁰. However, the underlying mechanisms behind this observation remain unclear. Recently, specialized pro-resolving mediators derived from omega-3 fatty acids were identified in self-limited models of acute inflammation and termed resolvins (*resolution phase interaction products*)^{95,101}. Similar to LXs, resolvins can be generated via ALOX5 catalyzed reactions during transcellular biosynthesis (reviewed in ⁹²). Based on the omega-3 fatty acid of origin, resolvins are divided into the D-series (docosahexaenoic acid; DHA, C22:6) or E- series (eicosapentaenoic acid; EPA, C20:5). Dietary modification or transgenic expansion of the *fat-1* gene (GeneID: 178291 (NC_003282.5)), which encodes a prokaryote omega-3 fatty acid desaturase, can increase resolvin production^{35,53}.

Resolvin E1

Resolvin E1 (RvE1) is present in resolving exudates⁹⁵ and lung¹⁶. RvE1 transcellular biosynthesis occurs in human vasculature in the presence of ASA with transformation of EPA to 18*R*-HEPE (18*R*-hydroxyeicosapentaenoic acid) by ASA-acetylated COX-2 in

endothelial cells⁷. 18R-HEPE is subsequently converted by leukocyte ALOX5 to RvE1 via a 5(6) epoxide-containing intermediate^{7,95}. RvE1 biosynthesis in humans can be increased by ingestion of ASA (100g) and/or following dietary EPA supplementation (1g)⁷. The stereochemical assignment for RvE1 is 5*S*,12*R*,18*R*-trihydroxyeicosa-6*Z*,8*E*,10*E*,14*Z*,16*E*-pentaenoic acid^{7,95}, and structure-activity relationships have established that RvE1's actions are highly stereoselective⁹².

Resolvin E1 Receptors

Receptors RvE1 have been recently identified^{7,8}. RvE1 interacts with the G-protein coupled receptor CMKLR1 as an agonist. CMKLR1 (aka ChemR23) was first identified as a receptor for the peptide chemerin. Thus, like ALX/FPR2, this receptor also recognizes both lipid and peptide ligands. CMKLR1 is expressed on monocytes/macrophages and plasmacytoid dendritic cells^{27,81,115}. Human CMKLR1 binds RvE1 with high affinity ($K_d = 11.3 \pm 5.4$ nM)⁷. RvE1 also interacts with a second G-protein coupled receptor: leukotriene B₄ receptor 1 (BLT1)⁸. In humans, BLT1 receptors are expressed by neutrophils, eosinophils, monocytes/macrophages, mast cells, dendritic cells, and effector T cells¹²⁰. RvE1 effectively competes with LTB₄ for BLT1 binding to functionally antagonize LTB₄-mediated responses⁸. RvE1's affinity for BLT1 ($K_d = 45$ nm) is relatively lower than for CMKLR1 and in addition to LTB₄ antagonism, RvE1 can serve as a partial agonist for BLT1 signaling.

Resolvin E1 in allergic airway responses and asthma

Resolvin E1 has potent anti-inflammatory and pro-resolving actions in a number of murine models of inflammation and is bioactive in very low concentrations (nanomolar to picomolar) *in vivo and in vitro*⁹⁵. RvE1 dampens the development and promotes the resolution of allergic airway responses in a murine experimental model of asthma^{3,50,51}. In nanogram quantities, intravenous administration of RvE1 decreases eosinophil and lymphocyte accumulation and airway mucous metaplasia and improves airway hyper-responsiveness to inhaled methacholine⁵¹. To promote resolution of inflammation, RvE1 decreases IL-6, IL-17 and IL-23 in the lung while increasing IFN- γ and LXA₄ formation⁵¹. RvE1's actions were additive with those of LXs, as these pro-resolving mediators both regulate IL-17. Of interest, only RvE1, and not LXA₄, regulated IL-23 and IFN γ levels⁵¹. Together, these findings support the presence of independent pro-resolving signalling circuits for RvE1 and LXA₄ that converge on the regulation of IL-17 to hasten catabasis in this model of allergic asthma exacerbations. RvE1 is also bioactive when given intraperitoneally before and during the sensitization and aeroallergen challenge phases of this asthma model³. Administration with RvE1 concurrent with allergen challenge can prevent the development of bronchial hyper-responsiveness, mucous metaplasia, eosinophil accumulation and T-helper type 2 (Th2) cytokine mediator release [*e.g.* IL-13].³ Because immune responses are pathologically sustained in asthma, models of self-limited allergic airway responses have been used to determine mechanisms for down-regulating adaptive immune responses in health with the goal of establishing the critical checkpoints for maintaining lung tissue homeostasis. In a murine model of asthma exacerbation with self-limited allergic airway inflammation, natural killer (NK) cell phenotype and trafficking to draining mediastinal lymph nodes is temporally regulated during resolution in a CXCL9-CXCR3 (ligand-receptor) dependent manner⁵⁰. Depletion of NK cells disrupts the endogenous resolution program, leading to delayed resolution of airway eosinophils and antigen specific CD4⁺ T cells, increased LTB₄ and interleukin-23, and decreased LXA₄⁵⁰. In addition, NK cells express CMKLR1 and RvE1 mediated resolution is markedly inhibited in this setting by NK cell depletion. These findings indicate new functions for NK cells in promoting resolution of adaptive immune responses and suggest that NK cells are targets for

specialized pro-resolving mediators for clearance of activated T cells from inflamed lung. No published reports are currently available for Resolvin E1 in human asthma.

Protectin D1

DHA is also present in resolving exudates and DHA is converted into D-Series resolvins¹⁰¹. Of interest, the DHA metabolome includes several additional classes of pro-resolving mediators, including protectins and maresins^{98,104}. Mucosal surfaces, including the airway, are enriched with DHA⁴¹, and airway mucosal epithelial cells from individuals with asthma or cystic fibrosis have depleted stores of DHA compared with healthy control subjects⁴¹. This section will focus on protectin D1 (PD1). Roles for D-Series resolvins, maresins and other DHA derived mediators in asthma is the subject ongoing research; however, there is currently only limited information on these compounds in asthma.

At sites of inflammation, DHA is rapidly converted by LOX activity to a 17*S*-hydroperoxy-containing intermediate and via an epoxide containing intermediate to protectins, such as PD1 (10*R*,17*S*-dihydroxy-docosa-4*Z*,7*Z*,11*E*,13*E*,15*Z*,19*Z*-hexaenoic acid).⁹⁹ When produced in neural systems this bioactive mediator is coined neuroprotectin D1 NPD1/PD1 (for detailed reviews, see^{13,92,94}). NPD1/PD1 is distinguished from D-Series resolvins by the presence of a conjugated triene and two alcohol groups in a specific chirality required for potent bioactions. Structure-activity relationships suggest that PD1's actions are receptor-mediated in human leukocytes⁶⁹; however, the PD1 receptor has yet to be molecularly characterized.

Protectin D1 in allergic airway responses and asthma

DHA can be delivered during the early stages of an acute inflammatory response in albumin-rich edema fluid⁵⁶. It is noteworthy that the cellular components of the airway mucosa are enriched with DHA⁴⁰ and both 17*S*-HDHA (17*S*-hydroxy-docosa-4*Z*,7*Z*,11*E*,13*E*,15*Z*,19*Z*-hexaenoic acid) and PD1 are generated in human airways⁶⁵. Of interest, PD1 levels decrease during acute exacerbations of asthma (Table 2) and PD1 mediates bronchoprotective actions in a murine experimental model of allergic asthma *in vivo*⁶⁵. Using ovalbumin-sensitized mice, PD1 (2 - 200 ng) given by the intravenous route prior to aeroallergen challenge markedly suppressed bronchial hyper-responsiveness, mucous metaplasia, pulmonary eosinophil accumulation and pro-inflammatory cytokine and lipid mediator release. PD1 also mediates pro-resolving actions on established pulmonary inflammation when given after allergen challenge, leading to significantly expedited resolution of allergic airway inflammation.⁶⁵ In a head to head comparison with a lipoxin stable analog and RvE1 in acute, self-limited murine peritonitis, PD1 displayed the lowest $\Psi_{\max}$ (maximum number of infiltrating leukocytes) and $T_{\max}$ (time to resolve) and the shortest R_1 (resolution interval, time taken from maximal leukocyte infiltration to 50% of maximum), indicative of PD1's potent bioactions¹².

Summary and Conclusions

The resolution of inflammation is an integral and natural part of the physiological response to tissue injury, infection and allergen or other noxious stimuli. Resolution is an active process with highly regulated cellular and biochemical events. Several discrete families of natural small molecules have recently been uncovered using a lipidomics approach. Select members are pro-resolving and stimulate tissue catabasis. These include resolvins, protectins and most recently maresins. Insights into these chemical mediators and their signaling pathways provide an opportunity to develop agonists of resolution as a potential novel class of therapeutics. The chronic and uncontrolled airway inflammation that characterizes asthma, especially severe variants of the disease, appears to result in part from a defect in

resolution. It is notable that in uncontrolled asthma there is also a defect in the generation of specialized pro-resolving mediators, including LXA₄ and PD1. Thus, bioactive stable analog mimetics of these mediators that can harness endogenous resolution mechanisms for inflammation may offer new therapeutic strategies for asthma and airway inflammation associated diseases.

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List of Abbreviations

12-LO	12-lipoxygenase
15(R)-HETE	15(R)-hydroxyeicosatetraenoic acid
15(S)-H(p)ETE	15(S)-hydroperoxyeicosatetraenoic acid
15-LO	15-lipoxygenase
15-PGDH	15-hydroxyprostaglandin dehydrogenase
5-LO	5-lipoxygenase
AhR	aryl hydrocarbon receptor
ASA	acetylsalicylic acid
ATLa	aspirin-triggered lipoxin analog
BALF	bronchoalveolar lavage fluid
C20:4	arachidonic acid
C20:5	eicosapentaenoic acid (EPA)
C22:6	docosahexaenoic acid (DHA)
COX-2	cyclooxygenase-2
CysLTs	cysteinyl leukotrienes
LSP-1	leukocyte specific protein-1
LTA₄	leukotriene A ₄
LTA₄H	leukotriene A ₄ hydrolase
LTC₄	leukotriene C ₄
LXA₄	lipoxin A ₄
PD1	protectin D1 (10 <i>R</i> ,17 <i>S</i> -dihydroxy-docosa-4 <i>Z</i> ,7 <i>Z</i> ,11 <i>E</i> ,13 <i>E</i> ,15 <i>Z</i> ,19 <i>Z</i> -hexaenoic acid)
PGs	prostaglandins
PMNs	polymorphonuclear leukocytes

Rv	resolvin
RvD1	Resolvin D1 (7 <i>S</i> ,8 <i>R</i> ,17 <i>S</i> -trihydroxydocosa-4 <i>Z</i> ,9 <i>E</i> ,11 <i>E</i> ,13 <i>Z</i> ,15 <i>E</i> ,19 <i>Z</i> -hexaenoic acid)
RvE1	Resolvin E1 (5 <i>S</i> ,12 <i>R</i> ,18 <i>R</i> -trihydroxyeicosa-6 <i>Z</i> ,8 <i>E</i> ,10 <i>E</i> ,14 <i>Z</i> ,16 <i>E</i> -pentaenoic acid)
SPM	specialized pro-resolving mediators

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Key Points

1. Resolution of inflammation is an active process with specific cellular and molecular events.
2. Specialized pro-resolving mediators are enzymatically derived from polyunsaturated fatty acids, including the omega-3 fatty acids EPA and DHA.
3. Pro-resolving mediators interact with specific receptors to regulate allergic airway responses and asthma.
4. Uncontrolled asthma is associated with a defect in pro-resolving mediator signaling.

Table 1

Cellular actions of pro-resolving mediators

Pro-resolving mediator	Cell type	Action	Reference
Lipoxin A ₄	Eosinophils	Inhibits of eosinophil migration	10
	T cells	Inhibits of TNF release	4
	Neutrophils	Inhibits PMN chemotaxis	102
		Inhibits trans-endothelial migration	34,76
		Inhibits trans-epithelial migration	34
		Inhibits of superoxide anion generation	64
		Inhibits of azurophilic granule release	108
	NK cells	Inhibits NK cell cytotoxicity	80
	Monocytes	Increases adhesion and transmigration	67
		Inhibits IL-8 released induce by TNF	20
	Macrophages	Increases engulfment of apoptotic PMN	46
	Smooth muscle	Inhibits LTC ₄ -initiated migration	77
	Endothelium	Stimulates prostacyclin release	22
	Epithelial cells	Increases proliferation after acid injury	18
		Inhibits cytokine release	18
		Increases intracellular Ca ²⁺	19
Resolvin E1	T cells	Increases CCR5 expression	5
	Neutrophils	Inhibits of trans-endothelial migration	25
Protectin D1	T cells	Increases CCR5 expression	5
	Neutrophils	Inhibits TNF α and IFN γ release	6
		Inhibits PMN trans-migration	12

Table 2

Uncontrolled asthma – A defect in pro-resolving mediators

Pro-resolving mediator	Evidence	Age	Country	Reference
Lipoxin A ₄	Aspirin-tolerant asthmatics generate more lipoxins than aspirin-intolerant asthmatics.	Adults	Poland	84
	Diminished lipoxin biosynthesis in severe asthma	Adults	USA	61
	Severe asthma is associated with a loss of LXA ₄ , an endogenous anti-inflammatory compound.	Adults	France	112
	Lipoxin A ₄ levels in asthma: relation with disease severity and aspirin sensitivity	Adults	Turkey	28
	Airway lipoxin A ₄ generation and lipoxin A ₄ receptor expression are decreased in severe asthma.	Adults	USA	78
	The role of lipoxin A ₄ in exercise-induced bronchoconstriction in asthma	Adults	Turkey	111
	Corticosteroid suppression of lipoxin A ₄ and leukotriene B ₄ from alveolar macrophages in severe asthma.	Adults	UK	15
	Reversed changes of lipoxin A ₄ and leukotrienes in children with asthma in different severity degree.	Children	China	118
Protectin D1	Generated in asthma and dampens airway inflammation and hyper-responsiveness.	Adults	US	65