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Bronchoprotective Mechanisms For Specialized Pro-Resolving Mediators in the Resolution of Lung Inflammation

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Abstract

Bronchi are exposed daily to irritants, microbes and allergens as well as extremes of temperature and acid. The airway mucosal epithelium plays a pivotal role as a sentinel, releasing alarmins when danger is encountered. To maintain homeostasis, an elaborate counter-regulatory network of signals and cellular effector mechanisms are needed. Specialized pro-resolving mediators (SPMs) are chemical mediators that enact resolution programs in response to injury, infection or allergy. SPMs are enzymatically derived from essential polyunsaturated fatty acids with potent cell-type specific immunoresolvent properties. SPMs signal by engaging cell-based receptors to turn off acute inflammatory responses and restore tissue homeostasis. Several common lung diseases involving the airways, including asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF), are characterized by unresolved bronchial inflammation. In preclinical murine models of lung disease, SPMs carry potent bronchoprotective actions. Here, we review cellular and molecular effects for SPM-initiated catabasis in the lung and their human translation.

Keywords

Lipoxins; Resolvins; Protectins; Maresins; Catabasis; Efferocytosis; Lung; Leukocytes; Airway; Mucosa

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Disclosure Statement

BDL is a co-inventor on patents assigned to Brigham and Women's Hospital. The interests of BDL were reviewed and are managed by the Brigham and Women's Hospital and Partners HealthCare in accordance with their conflict-of-interest policies. MGD and TRB have no pertinent interests to disclose.

1. Introduction

Inflammation is the body's response to injury or infection and manifests clinically as fever and in the lung as cough, sputum production, dyspnea and edema. Biologically, the initiation of acute inflammation results from a highly coordinated network of cellular and molecular events. Pro-inflammatory cytokines and chemokines and eicosanoids including leukotrienes and prostaglandins create a beacon of chemoattractants that results in leukocyte trafficking to sites of lung infection or injury. Endothelial and epithelial barriers become compromised by the inflammatory response creating tissue edema and purulent exudate (expectorated as sputum). Recruited granulocytes and lymphocytes then augment innate tissue-resident leukocytes and macrophages to contain and rid the body of the insult or invading pathogen. Initiating acute inflammation is vital for host protection and survival with many examples of immunosuppression increasing susceptibility to excess morbidity and mortality from infection. Equally important to health is the timely resolution of acute lung inflammation.

To counter the complexity and amplitude of pro-phlogistic mechanisms there exists endogenous resolution programs that are spatio-temporally regulated in the lung. Resolution is an active process designed to restore host tissues to a baseline non-inflamed state, a process termed catabasis. Inflammation resolution is orchestrated by several classes of mediators, including peptides, gases and lipids. Of particular relevance to this review is a superfamily of lipid mediators that are enzymatically-derived from dietary essential polyunsaturated fatty acids (PUFA). These specialized pro-resolving mediators (SPMs) include the arachidonic acid-derived lipoxins and the omega-3 fatty acid-derived resolvins, protectins, and maresins. (reviewed in (Serhan, 2014) and in Chapter XX/Serhan review for this special article). Each of the SPMs are stereoselective with structure activity relationships consistent with agonist properties at cognate receptors. During acute inflammation, lipid mediator class switching occurs as PUFA metabolism switches from pro-inflammatory mediators (*e.g.*, prostaglandins, leukotrienes) to pro-resolving mediators (*i.e.*, SPMs) (Levy et al., 2001). SPMs have cell-type specific and potent immunoresolvent actions to quench pro-inflammatory cytokine production by airway epithelial cells, increase epithelial production of anti-microbial peptides, halt leukocyte trafficking, and promote clearance of the inflammatory leukocytes through natural killer cell-mediated leukocyte apoptosis and macrophage phagocytosis of apoptotic leukocytes (Levy and Serhan, 2014). Thus, in health, SPMs promote the timely resolution of inflammation.

Chronic inflammation results from a failure of the body's resolution pathways to adequately turn off acute inflammatory responses and switch on mechanisms to restore homeostasis. Chronic unresolved inflammation underlies the pathophysiology of several common human lung diseases including asthma, chronic obstructive pulmonary syndrome (COPD), and cystic fibrosis (CF). Active research in humans and pre-clinical animal models of these diseases has uncovered a deficiency of SPMs and their tissue protective pro-resolving actions. Here, we review SPMs molecular, cellular, and biochemical bronchoprotective actions in response to acute inflammation of injury, infection and allergy with human translation in health and, when defective, in airway diseases.

2. SPM Bronchial Epithelial Actions

The airway mucosa is a first line of host defense against inhaled irritants, allergens, and pathogens. The epithelium provides a physical barrier against inhaled pathogens and toxins and initiates host immune responses through production of alarmins, inflammatory chemokines and cytokines that signal to cellular members of the innate and adaptive immune system. Epithelial cells are targets for regulation by SPMs that act to attenuate pro-inflammatory responses and promote epithelial restitution. In this section, we review SPM receptor expression on bronchial mucosal epithelial cells and SPM effects on the epithelium to resolve injury and promote host defense.

2.1. SPM Receptor Expression in the Human Airway

The pro-resolving and anti-inflammatory bioactions of SPMs stem from their signaling as agonists at specific receptors. To date, the molecular identify of five SPM receptors have been elucidated (Fig. 1).

2.1.1 ALX/FPR2—The lipoxin A_4/formyl peptide receptor 2 (ALX/FPR2) is a high affinity receptor for lipoxin A_4 (LXA_4) and a number of additional SPMs including 15-epi-LXA_4, resolvin D1 (RvD1) and aspirin-triggered-resolvin D1 (AT-RvD1) (Chiang et al., 2006; Fiore et al., 1994; Krishnamoorthy et al., 2012; Krishnamoorthy et al., 2010; Perretti et al., 2002). LXA_4 binding to ALX/FPR2 is stereoselective, specific, and reversible with a Kd of ~0.5 nM (Fiore et al., 1994; Fiore et al., 1992). ALX/FPR2 receptors can also engage and transmit signals from non-lipid ligands including annexin A1 (Chiang et al., 2006) and cathelicidin/LL-37 (Wan et al., 2011). Ligand recognition sites for lipids and peptides differ on ALX/FPR2 receptors and the ligands can trigger distinct downstream events that dramatically change the signaling properties of the receptor (Cooray et al., 2013). For example, 15-epi-LXA_4 is an allosteric inhibitor of serum amyloid A at ALX/FPR2 receptors and decreases cytokine production from airway epithelial cells (Bozinovski et al., 2012).

ALX/FPR2 is expressed on human and mouse airway epithelial cells as well as other cells directly related to inflammation at mucosal epithelial borders, including neutrophils, eosinophils, mast cells, monocytes, macrophages, lymphocytes, dendritic cells, innate lymphoid cells (ILCs), and natural killer (NK) cells (Barnig et al., 2013; Bonnans et al., 2006; Chiang et al., 2006; Fiore et al., 1994; Hua et al., 2014; Maddox et al., 1997; Miyazaki et al., 2014). ALX/FPR2 cellular expression is regulated locally by cytokines, transcription factors, and epigenetic mechanisms. LXA_4 itself binds to the ALX/FPR2 promoter and increases ALX/FPR2 expression in a positive feedback loop (Simiele et al., 2012). ALX/FPR2 expression is altered in several diseases of chronic inflammation. In severe asthma, ALX/FRP2 expression on granulocytes is decreased (Planaguma et al., 2008). In COPD lungs, epithelial ALX/FPR2 expression is increased in proximity to extrahepatic, submucosal serum amyloid A, and plasma pro-inflammatory ALX/FPR2 ligand serum amyloid A is produced in approximately 2-log order higher amounts than pro-resolving LXA_4, creating an imbalance towards a more pro-inflammatory state in COPD despite increased ALX/FPR2 expression (Bozinovski et al., 2012).

2.1.2 ERV—The E-series resolvin (ERV) receptor (also known as chemokine receptor-like 1 (CMKLR1) and chemerin receptor 23 (ChemR23)) is a high affinity receptor for resolvin E1 (RvE1) and likely resolvin E2 (RvE2) (Oh et al., 2012). Like ALX/FPR2, ERV can also engage non-lipid ligands, in particular chemerin, a chemoattractant peptide (Wittamer et al., 2003). ERV is expressed in the lung on airway epithelial cells and leukocytes, in particular those of the innate immune system, including neutrophils, monocytes, macrophages, dendritic cells, ILCs, and NK cells (Barnig et al., 2013; Campbell et al., 2007; Cash et al., 2013; Cash et al., 2008; Du and Leung, 2009; Herova et al., 2015; Parolini et al., 2007; Samson et al., 1998). ERV expression, in particular on NK cells, is highly regulated by cytokine expression in early phases of inflammation (Parolini et al., 2007). ERV signaling pathways may play an important role in protection against viral pathogens, as ERV knockout mice are particularly susceptible to viral respiratory pathogens with compromised viral clearance, increased lung leukocyte infiltration, compromised lung function, and increased mortality (Bondue et al., 2011).

2.1.3 BLT1—The leukotriene B_4 receptor 1 (BLT1) is expressed on inflammatory leukocytes including neutrophils, eosinophils, monocytes, macrophages, mast cells, dendritic cells, and lymphocytes (Yokomizo et al., 1997). Both RvE1 and RvE2 engage the BLT1 receptor as antagonists, competing with leukotriene B4 (LTB4) to counterregulate neutrophil chemotaxis, calcium mobilization, and NF-κB activation (Arita et al., 2007a). RvE1 blocks LTB4 binding at BLT1 to promote apoptosis of neutrophils and macrophage efferocytosis (El Kebir et al., 2012).

2.1.4 DRV1 and DRV2—The RvD1 receptor (DRV1; formerly GPR32) engages a number of activating lipid ligands including RvD1, AT-RvD1, RvD3, AT-RvD3, and RvD5 (Chiang et al., 2012; Dalli et al., 2013; Krishnamoorthy et al., 2012; Krishnamoorthy et al., 2010; Sun et al., 2007). DRV1 is expressed on human neutrophils, lymphocytes, macrophages, monocytes, and vascular tissues (Krishnamoorthy et al., 2010). Of note, RvD1 binds and engages DRV1 during periods of homeostasis whereas RvD1 interacts and signals through ALX/FPR2 during periods of resolving inflammation highlighting that SPMs can engage different receptors on different cell types in different physiologic states to exert spatiotemporally distinct effects.

The RvD2 receptor (DRV2; formerly GPR18) engages RvD2 to promote tissue resolution in a self-limited murine model of acute inflammation by promoting macrophage efferocytosis, enhancing phagocytosis of bacteria, and preventing neutrophil transmigration (Chiang et al., 2015). DRV2 is expressed mouse and human neutrophils, monocytes, and macrophages (Chiang et al., 2015).

2.1.5 Other SPM Receptors—Pharmacological structure activity relationships support that protectin D1 (PD1) and maresin 1 (MaR1) also exert their effects via receptor-dependent signaling mechanisms. PD1 binds sites on epithelial cells and neutrophils that are distinct from LXA_4 and RvE1 (Arita et al., 2007a; Marcheselli et al., 2010) and MaR1 can block the transient receptor potential V1 signaling to reduce neuropathic inflammation in mice (Serhan et al., 2012). The molecular identify of the receptors through which PD1 and MaR1 signal are still to be determined.

2.2. Epithelial Inflammation

The airway mucosal epithelium is one of the first points of host contact for invading pathogens and inhaled irritants and provides a physical barrier against such insults. The epithelial mucosa also plays a major role in initiating the inflammatory host immune response by producing alarmins, chemokines and cytokines that attract leukocytes to the site of epithelial injury or inflammation. Epithelial cells are also equipped with surface receptors for SPMs (*i.e.* ALX/FPR2 and ERV), the expression of which can be regulated by cytokines, in particular IL-13 and IFN-γ (Gronert et al., 1998). SPMs can signal through receptors on epithelial cells to deactivate inflammatory pathways and activate pro-resolution pathways. LXA_4 inhibits epithelial cell interactions with neutrophils and also inhibits the trans-epithelial migration of neutrophils (Bonnans et al., 2006; Colgan et al., 1993; Serhan et al., 1995). Of interest, the inhibition of 15-epi-LXA_4 production by a *Pseudomonas aeruginosa*-derived epoxide hydrolase cif in a murine model of cystic fibrosis (CF) promotes trans-epithelial migration of neutrophils (Flitter et al., 2017). LXA_4 treatment also protects against *P. aeruginosa* invasion in CF bronchial epithelial cells by preventing tight junction disruption (Higgins et al., 2016). In acute exacerbations of COPD, there is an imbalance in levels of serum amyloid A and LXA_4. Human bronchial epithelial cells exposed to serum amyloid A release inflammatory mediators, notably IL-8, a neutrophil chemo-attractant (Bozinovski et al., 2012). LXA_4 interacts with ALX/FPR2 to allosterically inhibit serum amyloid A-mediated IL-8 production by epithelial cells (Bozinovski et al., 2012). In a murine model, 15-epi-LXA_4 opposes the actions of serum amyloid A at ALX/FPR2 and significantly blocks epithelial cell-derived chemokines and reduces trans-epithelial cell migration of neutrophils (Bozinovski et al., 2012). Like LXA_4, RvD1 (Eickmeier et al., 2013; Wang et al., 2011), RvE1 (Campbell et al., 2007; Seki et al., 2010), and MaR1 (Krishnamoorthy et al., 2014) can also inhibit trans-epithelial migration of neutrophils in murine models of lung infection and injury. In addition to direct effects on inhibiting leukocyte transmigration and inhibiting leukocyte chemoattractant production, SPMs can also exert effects that have downstream effects on inflammation. In particular, RvD1 and AT-RvD1 downregulate the NF-κB signaling pathway in bronchial epithelial cells (de Oliveira et al., 2015; Hsiao et al., 2014) that can have significant effects on modulating lymphocyte differentiation and function.

2.3. Epithelial Injury

SPMs are also active in promoting repair of the mucosal epithelial barrier after injury. For example, aspiration of gastric acid evokes inflammatory responses by injured mucosal epithelial cells and infiltrating neutrophils and SPMs are pivotal mediators *in vivo* for promoting resolution of acid-induced acute lung injury in murine models. LXA_4 is produced *in vivo* in response to acid-initiated lung injury and blocks acid-triggered IL-6 release from bronchial epithelial cells and inhibits neutrophil transmigration across bronchial epithelial cells (Bonnans et al., 2006). LXA_4 also stimulates epithelial repair after acid injury by increasing basal epithelial cell proliferation (Bonnans et al., 2006). Injured bronchial epithelial cells upregulate ALX/FPR2 to promote LXA_4-mediated effects on epithelial repair after acid injury (Bonnans et al., 2006). AT-RvD1 and AT-RvD3 both act to improve epithelial barrier integrity after acid-initiated lung injury and promote catabasis by decreasing alveolar edema and epithelial permeability, neutrophil infiltration and pro-

inflammatory cytokines, and inhibiting NF-κB activation (Colby et al., 2016; Eickmeier et al., 2013). AT-RvD3 also promotes re-epithelialization after acid injury by increasing levels of keratinocyte growth factor and epithelial cell proliferation (Colby et al., 2016). In addition to macrophages, MaR1 is biosynthesized in the lung by neutrophil-platelet aggregates within hours after acid lung injury and protects against neutrophil infiltration, tissue edema, and pro-inflammatory cytokine production (Krishnamoorthy et al., 2014). MaR1 also modulates pro-inflammatory cytokine production from bronchial epithelial cells exposed to organic dust through mechanisms independent of the NF-κB signaling pathway (Nordgren et al., 2013).

2.4. Epithelial Host Defense

In addition to their effects on coordinating host cellular immune responses through chemokine and cytokine secretion, airway epithelial cells also express a number of antimicrobial factors that mediate additional host protective effects and also stimulate re-epithelialization to restore epithelial barrier integrity. Mucosal epithelial cells express bactericidal/permeability-increasing protein (BPI), a molecule that neutralizes bacterial endotoxin and kills gram negative bacteria (Canny et al., 2002). Lipoxins upregulate BPI expression in epithelial cells and increase mucosal bacterial killing (Canny et al., 2002). RvE1 enhances gastrointestinal mucosal epithelial cell alkaline phosphatase, which detoxifies bacterial lipopolysaccharide and impedes bacterial cell growth (Campbell et al., 2010). RvE1 also promotes epithelial cell expression of CD55, an anti-adhesive molecule that augments apical neutrophil clearance to resolve mucosal inflammation (Campbell et al., 2007). Finally, a number of SPMs reduce epithelial barrier disruption and protect against epithelial cell apoptosis (de Paiva et al., 2012; Erdinest et al., 2014; Mukherjee et al., 2004; Wang et al., 2012). These distinct actions of SPMs on mucosal epithelial cells provide another layer of antimicrobial host defense and regulation of pathogen-mediated airway inflammation.

2.5 Other Structural Cells and Innate Leukocytes in the Bronchi

SPMs can also exert effects on structural cells in the bronchi including pulmonary bronchi, airway smooth muscle, and fibroblasts. *In vitro*, LXA_4 mediates the relaxation of pulmonary bronchi and arterioles in isolated lung strips that are pre-contracted with leukotrienes (Dahlen et al., 1988) and inhibits leukotriene-mediated airway smooth muscle migration (Parameswaran et al., 2007). LXA_4 also regulates human lung fibroblast proliferation in response to connective tissue growth factor, a leading mediator of lung fibrosis (Wu et al., 2006). Together these studies demonstrate that SPMs actions on airway structural cells can counter-regulate pathological bronchial responses, including bronchoconstriction, airway smooth muscle hypertrophy, and fibrosis.

A number of innate leukocytes express SPM receptors and are targets for regulation by SPMs. Natural killer (NK) cells express ALX/FPR2 receptors and LXA_4 exposure increases NK cell mediated apoptosis of neutrophils and eosinophils (Barnig et al., 2013) thus promoting granulocyte removal for resolution. NK cells also express the SPM receptor ERV and depleting NK cells inhibits RvE1-mediated resolution of eosinophilic allergic lung inflammation *in vivo* (Haworth et al., 2011). Type 2 innate lymphoid cells (ILC2) express

ALX/FPR2 and ERV receptors and LXA_4 and MaR1 exposure both potently inhibit type 2 cytokine release from ILC2s (Barnig et al., 2013; Krishnamoorthy et al., 2014). Further, MaR1 promotes ILC2 amphiregulin production, a molecule with potent tissue restorative properties for restitution of inflammed or injured bronchial mucosal tissues (Krishnamoorthy et al., 2014). Mast cells are important producers of a variety of pro-phlogistic proteins and lipid mediators, including histamine, prostaglandins, and leukotrienes. Mast cells express SPM receptors, including ALX/FPR2 and BLT1 (Gastardelo et al., 2014; Lundeen et al., 2006). Notably, the lipoxins and D-series resolvins have mast cell stabilizing effects to block mast cell degranulation and histamine release (Karra et al., 2015; Martin et al., 2012).

3. Pre-clinical Models of Lung Disease

Pre-clinical models of lung diseases have consistently uncovered potent immunomodulatory roles for SPMs. Essential PUFA regulate the host inflammatory response to acute infection and injury through their conversion to bioactive lipid-derived mediators (Samuelsson et al., 1987). In response to tissue injury or infection, arachidonic acid (AA; C20:4*n*-6), docosahexaenoic acid (DHA; C22:6*n*-3) and eicosapentaenoic acid (EPA; C20:5*n*-3) are rapidly released from cellular phospholipids via phospholipase A2 enzyme activity (Murakami et al., 2011) or are carried via plasma exudate into inflammatory sites (Serhan, 2011). PUFAs can be detected within minutes of tissue injury in inflammatory exudates (Kasuga et al., 2008) where they are available for rapid enzymatic conversion to SPMs, including lipoxins, resolvins, protectins, and maresins (Serhan, 2014). In this section we focus on the role of SPMs in controlling inflammation in several examples of pre-clinical murine models of lung disease (Table 1).

3.1. Allergic Airway Disease

Asthma is a prevalent and complex disease of airway hyperresponsiveness, reversible airflow obstruction, inflammation and mucus metaplasia with several distinct phenotypes, including an allergic asthma phenotype characterized by type 2 inflammation and eosinophilia (Wenzel, 2012). In murine models of allergic airway inflammation, animals are first sensitized to an allergen (*e.g.* chicken ovalbumin (OVA)) for several weeks followed by an aerosol or direct airway challenge to simulate an allergen-induced asthma exacerbation. In allergen-sensitized mice, neutrophils, eosinophils, and lymphocytes are rapidly recruited to the lung within 12 hours of airway challenge and type 2 cytokines become elevated (Fig. 2A) (Flesher et al., 2014; Levy et al., 2002). The SPMs LXA_4 (Levy et al., 2002) and PD1 (Levy et al., 2007a) are also detected in the airways of allergen-sensitized mice, but at much lower levels than pro-inflammatory cysteinyl leukotrienes and prostaglandins (Levy et al., 2002). Murine models of allergic airway disease have been critical in unraveling the effects of SPMs on modulating allergen-induced lung inflammation and in promoting the resolution of host immune responses to allergen challenge.

3.1.1. SPM Effects on Prevention of Disease—LXA_4 and its stable analogs have significant prophylactic effects on preventing allergic pulmonary inflammation in murine models of allergic asthma (Levy et al., 2002; Levy et al., 2007b). Administration of a stable

LXA_4 analog to OVA-sensitized animals prior to allergen challenge significantly inhibits bronchoconstriction to methacholine, reduces eosinophil and lymphocyte lung infiltration, and reduces lung levels of type 2 cytokines IL-5 and IL-13 and pro-phlogistic mediators prostaglandins and cysteinyl leukotrienes (Levy et al., 2002). LXA_4 analogs can be designed to be active even when administered enterally and inhibit leukocyte trafficking and type 2 cytokine release in a mechanism distinct from cysteinyl leukotriene receptor antagonists such as montelukast (Levy et al., 2007b). LXA4 analogs are also effective at blunting airway inflammation and hyperreactivity when administered before allergen challenge in a cockroach allergen (CRA) model of allergic airway inflammation (Levy et al., 2007b). Further, LXA_4 prevents antigen-specific antibody production in OVA-sensitized mice, which hinders memory antibody responses after rechallenge, highlighting an additional mechanism by which LXA_4 regulates the host immune response (Ramon et al., 2014b).

Additional SPMs have also been shown to have effects on preventing allergic lung inflammation in animal models. Lipoxin B_4 (LXB_4), a structurally distinct member of the lipoxin family, decreases the number of infiltrating BAL eosinophils and lymphocytes in a dose-dependent manner when administered prior to allergen challenge in OVA-sensitized mice (Karra et al., 2015). RvD1 (Rogerio et al., 2012), RvE1 (Aoki et al., 2008; Arita et al., 2007b; Flesher et al., 2014), and PD1 (Levy et al., 2007a) all markedly abrogate the development of allergic airway responses in particular eosinophilia and lymphocyte recruitment, mucus metaplasia, and type 2 cytokine production when administered prophylactically to OVA-sensitized mice prior to allergen challenge. Maresin 1 (MaR1), a macrophage derived SPM, has potent counter-regulatory actions on the innate immune system (Krishnamoorthy et al., 2014). Prophylactic intravenous MaR1 administered to OVA-sensitized mice prior to allergen challenge reduces lung inflammation by inhibiting type 2 cytokine production by ILC2s (Krishnamoorthy et al., 2014).

3.1.2. Pro-resolving Actions of SPMs—SPMs also have potent actions to promote the resolution of inflammation when administered in a therapeutic manner after allergen challenge when the host immune response has already been established (Fig. 2B). Treatment of OVA aerosol challenged mice in the post-challenge phase with a stable 15-epi-LXA_4 analog significantly reduces airway inflammation by reducing BAL leukocyte numbers and IL-17 levels (Haworth et al., 2008). Lipoxin B_4 (LXB_4) promotes the resolution of allergic inflammation in both the upper and lower airways. LXB_4 significantly reduces nasal mucosal inflammation, IgE and type 2 cytokine levels, leukocyte infiltration, eosinophil and mast cell degranulation, and mucin secretion in a murine model of allergic rhinitis (Karra et al., 2015). In the lower airways, LXB_4 treatment of allergen-challenged mice significantly accelerates the resolution of allergic inflammation by approximately 30% by decreasing BAL eosinophils, macrophages, and lymphocyte numbers and decreases airway hyper-responsiveness (Karra et al., 2015). RvD1 and AT-RvD1 treatment of allergen-challenged mice similarly accelerates the resolution interval for lung eosinophilia and blunts airway hyperresponsiveness to methacholine while also enhancing macrophage phagocytosis and clearance of allergen (Rogerio et al., 2012). Similarly, PD1 treatment after allergen challenge accelerates the resolution phase of lung inflammation and dampens type 2 cytokine production (Levy et al., 2007a). In acute and chronic allergic inflammation models,

RvE1 treatment promotes the resolution of host lung inflammation similarly to other SPMs by restraining eosinophil and lymphocyte recruitment and suppressing inflammatory cytokine production (Aoki et al., 2008; Flesher et al., 2014; Haworth et al., 2008). In addition, RvE1 treatment in allergic inflammation increases lipoxin formation and directly inhibits IL-23 and IL-17 production in the lung (Haworth et al., 2008) and promotes natural killer cell cytotoxicity (Haworth et al., 2011), supporting a role for RvE1 in modulating additional inflammatory pathways to promote resolution of allergic lung inflammation. MaR1 administered therapeutically after allergen challenge exhibits anti-inflammatory and pro-resolving actions to regulate innate immune responses (Krishnamoorthy et al., 2014, 2015). MaR1 treatment increases Foxp3+ regulatory T cell numbers and suppressive actions in a TGF-β- dependent manner that restrains type 2 cytokine production by ILC2 and increases amphiregulin production, which together promotes the resolution of allergic lung inflammation (Krishnamoorthy et al., 2014, 2015).

3.2. Acute Lung Injury

Acute lung injury results in leukocyte trafficking to the lung to protect the host and restore tissue homeostasis. If excessive, lung leukocyte infiltration from the acute inflammatory response can result in the overwhelming and deleterious lung inflammation seen in the acute respiratory distress syndrome (ARDS), a pathologic condition in which the leukocyte-rich exudate fills alveoli and prevents adequate oxygenation with high rates of morbidity and mortality (Baron and Levy, 2016). Human clinical trials have failed to demonstrate effective treatments for ARDS that target the overabundant host inflammatory response. Therapies harnessing SPMs to promote inflammation resolution represent a new treatment strategy and in murine models of acute lung injury SPMs have shown promise in controlling inflammation from lung injury.

3.2.1. SPM Effects on Prevention of Disease—Pre-injury administration of 15-epi-LXA_4 decreases lung neutrophil recruitment in a murine model of aspiration pneumonia (Planaguma et al., 2010). Lovastatin triggers 15-epi-LXA_4 formation and when present can lessen the severity of lung injury (Planaguma et al., 2010). AT-RvD1 prophylaxis decreases peak BAL inflammatory neutrophil infiltration by ~75%, inhibits platelet-neutrophil interactions, improves barrier integrity, and decreases airway resistance in a murine acid aspiration model (Eickmeier et al., 2013). Similarly, RvE1 prophylaxis significantly decrease peak BALF inflammatory leukocyte infiltration in a murine model of acid injury while also enhancing bacterial clearance and decreasing lung levels of pro-inflammatory cytokines, resulting in marked improvement in survival (Seki et al., 2010).

3.2.2. Pro-resolving Actions of SPMs—Resolution of acute acid-induced lung injury requires intact signaling of LXA_4 and 15-epi LXA_4 through ALX/FPR2 receptors and is impaired when COX-2 activity is inhibited (Fukunaga et al., 2005). Exogenous treatment with AT-RvD1 or AT-RvD3 after acid injury in murine models reduces neutrophil tissue infiltration and alveolar edema and promotes bronchial epithelial repair (Colby et al., 2016; Eickmeier et al., 2013). RvD2 potently regulates systemic inflammatory responses and local tissue leukocyte trafficking in sepsis (Spite et al., 2009), a common cause of acute lung injury and ARDS in humans. Finally, MaR1 is organ protective in a murine model of acid-

induced acute lung injury (Abdulnour et al., 2014). In addition to macrophages, early MaR1 production is dependent on platelet-neutrophil interaction and when given exogenously 1 hour after acid-induced lung injury, MaR1 significantly reduces lung edema, neutrophil infiltration, and pro-inflammatory cytokine production leading to improved lung function (Abdulnour et al., 2014).

3.3. Bacterial Lung Infection

Bacterial pneumonia is a common disease in humans and for the majority of individuals is a self-limited and mild disease. With some particularly virulent microbes or in a subset of susceptible patients, bacterial pneumonia evolves into respiratory failure and ARDS characterized by overwhelming inflammation that compromises oxygenation and ventilation and leads to high rates of morbidity and mortality (Baron and Levy, 2016). Studies of SPMs in murine models of bacterial pneumonia have highlighted beneficial preventative and treatment effects of SPMs on host lung defense and inflammation.

3.3.1. SPM Effects on Prevention of Disease—In a murine model of lipopolysaccharide (LPS)-induced acute lung injury, RvD1 administered prior to LPS exposure was protective resulting in decreased lung leukocyte trafficking, inhibition of pro-inflammatory cytokine secretion, and decreased mortality (Wang et al., 2011). Prophylactic RvE1 also blunts host inflammation in a murine model of aspiration pneumonia (Seki et al., 2010). Animals pretreated with intravenous RvE1 prior to intratracheal instillation of hydrochloric acid followed by *Escherichia coli* had 50% reduced recruitment of neutrophils to the lung, reduced bacterial burden, decreased pro-inflammatory cytokines, and enhanced survival (Seki et al., 2010).

3.3.2. Pro-resolving Actions of SPMs—SPM treatment of animals with bacterial pneumonia also promotes the timely resolution of the host inflammatory response. LXA_4 and RvE1 both promote neutrophil phagocytosis-induced apoptosis to accelerate resolution of pulmonary inflammation and improve survival in a murine model of *E. coli* pneumonia (El Kebir et al., 2012; El Kebir et al., 2009). Early treatment with RvD1 within one hour of infection with *E. coli* or *Pseudomonas aeruginosa* enhances lung macrophage phagocytosis of bacteria and efferocytosis of neutrophils *in vivo* and promotes macrophage phagocytosis of *E. coli* particles in *ex vivo* lung sections (Abdulnour et al., 2015). Moreover, the combination of RvD1 and antibiotics has additive effects on enhancing bacterial clearance (Abdulnour et al., 2015). These studies provide evidence that SPMs could provide a potent augmentative therapeutic approach to treating bacterial pneumonia that harnesses mechanisms targeting both the host and the microbe to enhance pathogen clearance, mitigate leukocyte activation and trafficking to the lung, and promote efferocytosis of apoptotic leukocytes to restore the lung to a homeostatic state.

3.4. Viral Lung Infection

Viral pulmonary infections are a dominant cause of respiratory illnesses in particular in the pediatric and elderly populations and treatment is largely limited to supportive care. Most common viral pathogens generate self-limited and mild infections but highly virulent strains can result in overwhelming pulmonary inflammation that can lead to critical illness and even

death (Thompson et al., 2003). Influenza is a seasonal pathogen with notable severely pathogenic strains that have resulted in global pandemics with excess mortality (*i.e.* the 1918 and 2009 H1N1 pandemics). In murine models of influenza, SPMs are inversely correlated with the virulence of the influenza strain. The more virulent strains of virus (*i.e.* H5N1) are associated with decreased levels of lipoxins (Cilloniz et al., 2010) and protectin D1 (Morita et al., 2013) with increased lung leukocyte recruitment, and lethal viral dissemination.

3.4.1. SPM Effects on Prevention of Disease—When administered prophylactically intravenously 12 hours prior to infection, PD1 markedly inhibits influenza virus replication by interfering with the virus RNA nuclear export machinery, thereby inhibiting nuclear export of viral transcripts and resulting in improved survival in animals with severe disease (Morita et al., 2013). Further, the SPM 17-HDHA enhances virus-specific humoral immunity in a pre-clinical influenza vaccination model where animals vaccinated with both 17-HDHA and influenza proteins have superior protection against live viral challenge compared to animals immunized with viral antigens alone (Ramon et al., 2014a). In a pre-clinical model of respiratory syncytial virus (RSV) infection, pre-treatment of macrophages with LXA_4 or RvE1 prior to RSV infection promoted a pro-resolving macrophage phenotype (*i.e.* alternatively activated) for clearance of infection and inflammation and resolution of lung pathology (Shirey et al., 2014).

3.4.2. Pro-resolving Actions of SPMs—PD1 has therapeutic benefit even when administered after influenza infection has been established. Animals treated with PD1 48 hours after influenza infection exhibited improved pulmonary function and markedly improved survival compared to animals treated with the antiviral medication peramivir (Morita et al., 2013). Thus, PD1 had marked beneficial effects, both prophylactically and therapeutically, in an *in vivo* model of influenza infection. Of interest, engaging toll-like receptor 7 (TLR7), a receptor for viral single stranded RNA, triggers the generation of PD1 and RvD1 and enhances resolution of type 2 airway inflammation in mice (Koltsida et al., 2013). Together these studies suggest that SPMs are powerful agents to affect virus-host interactions and modify host- and pathogen-mediated lung pathology. Further studies, in particular in humans, are warranted.

4. Human Translation

SPMs are detectable in numerous human body fluids and tissues including peripheral blood, plasma and serum, bronchoalveolar lavage fluid and sputum, cerebrospinal fluid, breast milk, synovial joint fluid, and tears (Serhan, 2014). The levels of lipoxins, resolvins, and protectins in healthy human serum are in the picomolar to nanomolar range (Psychogios et al., 2011) and dietary supplementation with omega-3 fatty acids can increase serum SPM levels (Colas et al., 2014; Mas et al., 2012; Psychogios et al., 2011). Common airway diseases such as asthma and COPD are characterized by chronic inflammation that fails to resolve. In this section, we review studies that have identified deficiencies in SPMs in these common human lung diseases (Table 2). Together, this body of evidence suggests that insufficient levels and activity of SPMs in the resolution phase of inflammation may prolong acute inflammatory responses and contribute to the persistent inflammation in the lungs of patients with these chronic diseases.

4.1. Asthma

Asthma is a chronic disease of unrestrained airway inflammation and hyperresponsiveness that is triggered by irritant, allergic, and infectious stimuli resulting in an influx of inflammatory leukocytes (in particular eosinophils, neutrophils, and lymphocytes) and pro-inflammatory mediators (*e.g.*, type 2 cytokines) to the airway (Fahy, 2015). Approximately 10% of patients have severe asthma characterized by daily symptoms and uncontrolled disease despite high dose inhaled and/or systemic corticosteroids (Wenzel, 2012).

4.1.1 Deficiency of SPMs in Asthma—Severe asthma patients have decreased levels of LXA_4 in blood, BALF, induced sputum, and exhaled breath condensates that correlates with disease severity and compromised lung function (Table 2) (Bhavsar et al., 2010; Celik et al., 2007; Fritscher et al., 2012; Kazani et al., 2013; Levy et al., 2005; Planaguma et al., 2008; Vachier et al., 2005). Decreased lipoxin generation in uncontrolled asthma is at least partially attributable to dysregulated lipoxin biosynthetic genes (Planaguma et al., 2008). Further, lipoxin levels are also decreased in severe asthma as a consequence of oxidative stress (Ono et al., 2014). Patients with aspirin-exacerbated respiratory disease also have decreased LXA_4 biosynthesis and elevated leukotriene levels suggesting that an imbalance in pro-inflammatory and pro-resolving mediators underlies the pathogenesis of this asthma phenotype (Celik et al., 2007; Sanak et al., 2000; Yamaguchi et al., 2011). In health, the airway mucosa is highly enriched with DHA; however, mucosal levels of DHA are reduced in asthma (Freedman et al., 2004) decreasing the amount of DHA locally available in the airway for conversion to DHA-derived SPMs, including D-series resolvins, protectins, and maresins. Indeed, levels of PD1 are decreased in exhaled breath condensates of uncontrolled asthmatic patients during acute exacerbations (Levy et al., 2007a) and eosinophil production of PD1 is reduced in severe asthma (Miyata et al., 2013).

4.1.2 Biologic Actions of SPMs in Asthma—Importantly, LXA_4 actions in blunting bronchoconstriction have been confirmed *in vivo* in humans (Table 3). In a human clinical trial, inhaled LXA_4 protects asthmatic patients from leukotriene-mediated bronchoprovocation (Christie et al., 1992). Recent studies have demonstrated that LXA_4 can also modulate cellular immune responses in asthma. LXA_4 promotes pro-resolving functions of natural killer (NK) cells by enhancing NK cell-mediated apoptosis of neutrophils and eosinophils to terminate acute inflammation (Barnig et al., 2013). Further, IL-13 production by ILC2s is inhibited by LXA_4 (Barnig et al., 2013), supporting the potential therapeutic role for LXA_4 in dampening type 2 inflammation in asthma. Supplementing pregnant women with high doses of the n-3 PUFAs DHA and EPA reduces the incidence of persistent wheeze and asthma in their children by one-third (Bisgaard et al., 2016) lending further support to results in pre-clinical experimental models demonstrating the effectiveness of SPMs in mitigating the development and symptoms of asthma.

4.2. Chronic Obstructive Pulmonary Disease (COPD)

COPD is a chronic inflammatory lung disease triggered by cigarette smoke exposure that results in a pro-inflammatory environment in the lung with excess cellular and soluble mediators predisposing patients to recurrent exacerbations and progressive lung dysfunction (Pauwels and Rabe, 2004). Like asthma, COPD is a disease of unrestrained chronic lung

inflammation that can be refractory to the anti-inflammatory actions of corticosteroids and fails to resolve. The role of SPMs in regulating COPD pathogenesis is an area of active investigation.

4.2.1 Deficiency of SPMs in COPD—Moderate to severe COPD patients have reduced levels of LXA_4 (Fritscher et al., 2012) and LXB_4 (Croasdell et al., 2015) in exhaled breath condensates and elevated levels of pro-inflammatory leukotrienes (Table 2) (Vachier et al., 2005). During acute exacerbations in patients with COPD, LXA_4 levels are 2–3 log orders lower than serum amyloid A, which can pirate ALX/FPR2 receptors to promote inflammation and overwhelm LXA_4-mediated protective effects (Bozinovski et al., 2012). DHA-derived RvD1 levels in BALF and serum of COPD patients are also lower than in healthy individuals (Croasdell et al., 2015).

4.2.2 Biologic Actions of SPMs in COPD—SPMs have anti-inflammatory and pro-resolving effects on COPD pathophysiology *in vitro* (Table 3). Pharmacologic dosing of 15-epi-LXA_4 abrogates neutrophilic inflammation induced by intranasal SAA challenge in mice by reducing BALF neutrophil chemokine secretion and neutrophil recruitment by more than 50% (Bozinovski S, 2012). Of note, 15-epi-LXA_4 actions are distinct from the anti-inflammatory corticosteroid dexamethasone, which does not significantly alter airway neutrophilia after SAA challenge (Bozinovski S, 2012). RvD1 and AT-RvD1 are effective *in vitro* at dampening pro-inflammatory cytokine release from human alveolar macrophages isolated from COPD patients (Croasdell et al., 2015). RvD1 significantly inhibits neutrophilic lung inflammation and pro-inflammatory cytokine production elicited by smoke exposure and promotes an alternatively activated macrophage phenotype with enhanced capacity for neutrophil efferocytosis (Hsiao et al., 2013). Further, RvD1 also upregulates production of the anti-inflammatory cytokine IL-10 and accelerates the resolution of lung inflammation when administered after cessation of smoke exposure (Hsiao et al., 2013). RvE1 is also active at attenuating cigarette-smoke induced superoxide production and cell death in macrophages (Takamiya et al., 2012). Together, these studies highlight important mechanisms by which SPMs can influence macrophage phenotype and function to promote inflammation resolution and halt pro-inflammatory immune signals in this disease of chronic lung inflammation.

4.3. Cystic Fibrosis (CF)

CF is a genetic disease of dysfunctional chloride channels that affects multiple organs including the lungs, pancreas, GI tract and liver and leads to significant lifelong morbidities and early mortality. The lung pathology in CF is significant with tenacious mucus secretions that obstruct airways leading to hypoxemia and providing a nidus for bacterial infection. Patients with CF have recurrent airway infections and chronic airway inflammation that lead to destruction of airways and compromised lung function over time and result in frequent hospitalizations and eventually lung transplantation or death.

4.2.1 Deficiency of SPMs in CF—As in asthma and COPD, levels of LXA_4 in airway secretions are reduced in patients with CF (Table 2) (Karp et al., 2004; Yang et al., 2012). Moreover, *Pseudomonas aeruginosa*, a common pathogen amongst CF patients, inhibits 15-

epi-LXA_4 generation and function through the actions of a secreted epoxide hydrolase, thus promoting airway neutrophilia and impairing lung function (Flitter et al., 2017). Sputum LXA_4 levels can be increased in CF patients by antibiotic treatment correlating with decreased sputum neutrophils and IL-8 levels (Chiron et al., 2008). CF patients with detectable RvE1 have better lung function compared to patients with undetectable RvE1 levels who have the lowest lung function (Yang et al., 2012). Finally, mucosal DHA levels are also reduced in CF patients (Freedman et al., 2004) underscoring the broad deficiency of both precursor PUFAs as well as lipid-derived SPMs in CF.

4.2.2 Biologic Actions of SPMs in CF—In a murine model of CF, lipoxin treatment suppresses neutrophilic lung inflammation and decreases bacterial burden resulting in a less severe disease course (Table 3) (Karp et al., 2004). This study provides further evidence that leveraging lipoxins and other SPMs to target diseases of chronic lung inflammation may provide alternate therapeutic avenues for these morbid diseases.

4.4. Pediatric Considerations

Asthma is the most common chronic disease of childhood affecting nearly 10% of children in the United States, a current total of 7 million children (Akinbami et al., 2009). As in adult asthma, an imbalance in pro-inflammatory and pro-resolving mediators may contribute to the pathophysiology of pediatric asthma. LXA4 levels are reduced in exhaled breath condensates of asthmatic children admitted to a pediatric intensive care unit with status asthmaticus relative to healthy children (Hasan et al., 2012). Similarly, children with exercise-induced asthma have lower circulating plasma LXA_4 levels after exercise challenge relative to those children with asthma not triggered by exercise and LXA_4 levels are inversely correlated with lung function in these children (Tahan et al., 2008). Children whose mothers were supplemented with high doses of n-3 PUFA during pregnancy are one-third less likely to develop persistent wheeze and asthma compared to their peers whose mothers did not received fish oil supplementation (Bisgaard et al., 2016). This sentinel study underscores the importance of lipid-derived mediators in not only modulating the disease course of asthma but in preventing its development in children.

Mother-to-child transmission of SPMs through breast milk is a likely contributor to maternal-derived immune defense mechanisms for infants as breast milk is enriched in the n-3 PUFAs DHA and EPA (Peng et al., 2009). Human breast milk contains a biochemical profile rich in PUFA-derived SPMs including lipoxins, resolvins, protectins, and maresins at physiologically relevant levels (Arnardottir et al., 2016; Weiss et al., 2013). Human breast milk lipid mediator isolates are effective at stimulating the resolution of acute infectious peritonitis by regulating neutrophil trafficking, enhancing bacterial clearance, and shortening the resolution interval of acute inflammation as well as by enhancing human macrophage efferocytosis (Arnardottir et al., 2016). Taken together, these findings provide additional support for the health benefits of breastfeeding by highlighting a program of SPM-driven resolution of inflammation and infection that may provide another layer of immune protection for vulnerable infants.

Human clinical trials evaluating the efficacy of SPM compounds on ameliorating inflammation are beginning to be conducted. Recently, topical 15-epi-LXA_4 was shown to be as effective as topical steroids at relieving dermal inflammation in infants with eczema (Wu et al., 2013) supporting the therapeutic potential of SPM-based therapies in human disease. Topical RvE1 and LXA_4 analogs are currently being investigated in clinical trials focused on diseases of eye and periodontal inflammation (*e.g.*, NCT02329743, NCT02342691).

5. Conclusions

In health, the host airway immune response to invading pathogens, injury, allergen or other noxious stimuli is a spatiotemporally regulated network of cellular and molecular pathways whereby acute inflammatory responses are activated and once the threat is contained, an equally sophisticated resolution pathway is engaged to turn off inflammation for catabasis. With their anti-inflammatory and pro-resolving actions, the PUFA-derived endogenous SPMs are central to the body's counter-regulatory inflammation resolution program and help restore the host tissues to homeostasis. When the natural resolution pathways are interrupted or deficient, chronic inflammation ensues. Here, we have reviewed that the pathophysiology of several common and morbid diseases of bronchial inflammation, notably asthma, COPD, and CF, are linked to insufficient levels or activity of SPMs. Current therapies targeting lung inflammation rely heavily on medications that are anti-inflammatory in nature but are non-specific in their mechanism of action. For example, corticosteroids, used commonly as anti-inflammatory therapies in the treatment of asthma and COPD, have the unintended side effect of immunosuppression, which leaves the host at risk for infection and poor wound healing. Therapies that target lung inflammation and promote inflammation resolution without causing undesirable immunosuppression are greatly needed. Murine models of human inflammatory and infectious lung diseases have clearly demonstrated the efficacy of SPMs in promoting key pathways of inflammation resolution including inhibiting trans-epithelial leukocyte transmigration, reducing pro-inflammatory cytokine production, promoting macrophage efferocytosis, restoring epithelial barrier integrity, and improving lung function and survival. Human clinical trials of SPMs and the precursor PUFAs have demonstrated encouraging success in inhibiting bronchoprovocation in patients with asthma, preventing the development of asthma in children, and alleviating dermal irritation in infants with eczema (Bisgaard et al., 2016; Christie et al., 1992; Wu et al., 2013). In addition to the insights into lung physiology and disease pathogenesis provided by mapping of endogenous resolution pathways, leveraging the potent bronchial protective actions of SPMs to pharmacologically promote inflammation resolution and antimicrobial host defense without the untoward side effects (*i.e.* immunosuppression) of traditional anti-inflammatory medications would enhance our arsenal of therapies for common airway diseases of chronic lung inflammation, such as asthma, COPD, and CF.

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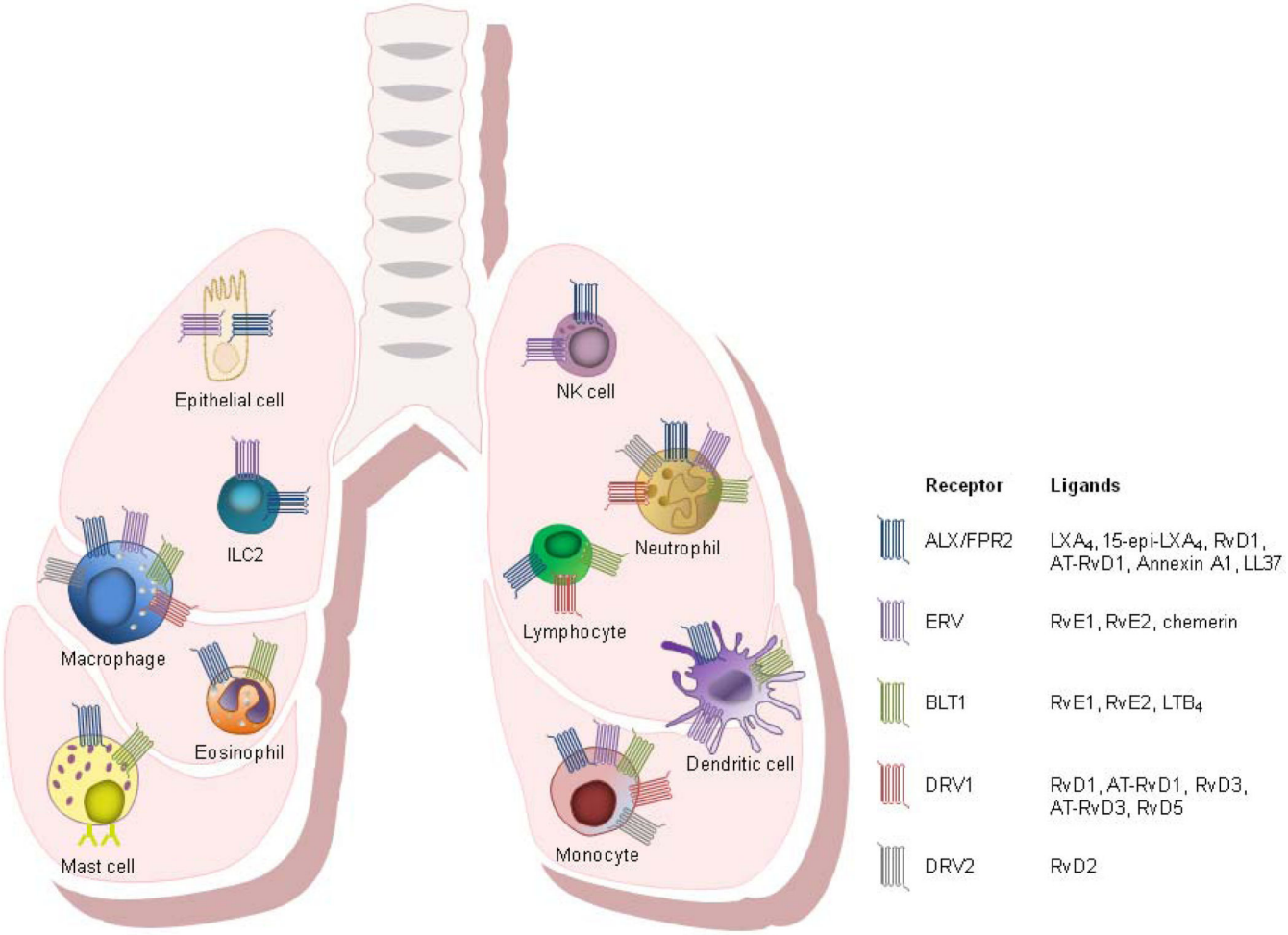

Fig. 1. Specialized Pro-Resolving Mediator Receptor Expression on Airway Epithelial Cells and Leukocytes

SPM receptors are expressed on human and mouse airway epithelial cells as well as other cells directly related to inflammation at mucosal epithelial borders, including neutrophils, eosinophils, mast cells, monocytes, macrophages, lymphocytes, dendritic cells, innate lymphoid cells (ILCs), and natural killer (NK) cells.

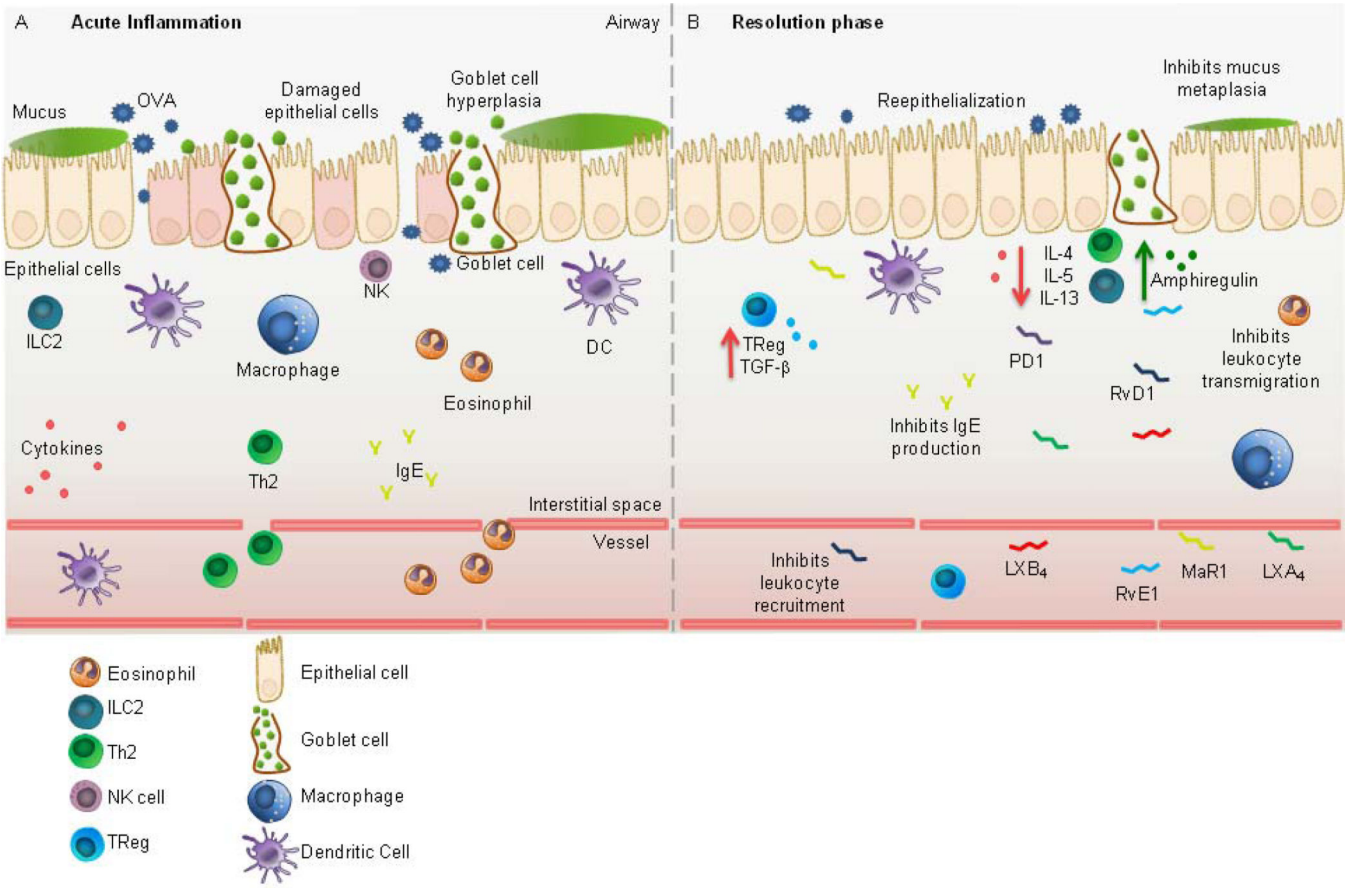

Fig. 2. Anti-Inflammatory and Pro-Resolving Bronchial Effects of SPMs in Allergic Asthma

(A) Allergic asthma is characterized histologically by inflammatory leukocyte infiltration and inflammatory cytokine release, goblet cell hyperplasia and mucus metaplasia, epithelial barrier disruption, and airway edema. **(B)** In the resolution phase, SPMs act via cell-specific mechanisms to halt inflammation and promote tissue homeostasis including restitution of epithelial barrier integrity, inhibition of mucus metaplasia, halting leukocyte trafficking, inhibiting type 2 cytokine release and promoting ILC2 amphiregulin production.

Table 1

Specialized Pro-Resolving Mediator Actions in Murine Models of Lung Diseases

Mediator	Actions	Reference
Allergic Airway Disease (Asthma and Rhinitis)		
LXA_4	Prevents airway hyperreactivity, Inhibits eosinophils and lymphocyte infiltration, reduces levels of IL-4, IL-5, IL-13, prostaglandins, and cysteinyl leukotrienes	Levy et al. 2002; Levy et al. 2007
	Prevents antigen-specific antibody production	Ramon et al. 2014
	Reduces BAL leukocyte numbers and IL-17 levels	Haworth et al. 2008
LXB_4	Prevents airway hyperreactivity, inhibits BAL eosinophil, macrophages and lymphocyte infiltration	Karra et al. 2015
	Reduces nasal mucosal and lower airway inflammation, IgE, type 2 cytokines, leukocyte infiltration, eosinophil and mast cell degranulation and mucin secretion	Karra et al. 2015
RvD1	Prevents airway hyperreactivity, inhibits BAL eosinophils and leukocyte infiltration, reduces IL-5 levels and mucus metaplasia, enhances macrophages phagocytosis and clearance of allergen; Accelerates resolution of lung eosinophils, reduces airway hyperresponsiveness	Rogerio et al. 2012
RvE1	Prevents airway hyperreactivity, reduces eosinophils and lymphocyte recruitment, IL-13 levels, antigen- specific antibody production and mucus metaplasia	Aoki et al. 2008
	Increases lipoxin formation and inhibits IL-17 and IL-23 production	Haworth et al. 2008
	Promotes NK cell cytotoxicity	Haworth et al. 2011
PD1	Prevents eosinophil and lymphocyte recruitment, reduces pro-inflammatory cytokines and mucus metaplasia and accelerates resolution of inflammation	Levy et al. 2007
MaR1	Promotes *de novo* generation of regulatory T cells, reduces type 2 cytokine and amphiregulin production by type 2 innate lymphoid cells	Krishnamoorthy et al. 2014
Acute Lung Injury		
LXA_4	Reduces neutrophil recruitment	Planaguma et al. 2010
RvD1	Reduces neutrophil infiltration, inhibits neutrophil-platelet interaction, improves barrier integrity and decreases airway resistance; Promotes epithelial repair	Eickmeier et al. 2013
RvD2	Regulates systemic inflammatory responses and local tissue leukocyte trafficking in sepsis	Spite et al. 2009
RvD3	Reduces neutrophil infiltration and alveolar edema and promotes epithelial repair	Colby et al. 2016
RvE1	Reduces BAL leukocytes, enhances bacterial clearance, decreases pro-inflammatory cytokines, improves survival	Seki et al. 2010
MaR1	Reduces lung edema, neutrophil infiltration, and pro-inflammatory cytokine production, improves lung function	Abdulnour et al. 2014
Bacterial Lung Infection		
LXA_4	Promotes neutrophil apoptosis, accelerates resolution of pulmonary inflammation, enhances survival	El Kebir et al. 2009
RvD1	Decreases lung leukocyte trafficking, inhibits pro-inflammatory cytokines and decreases mortality	Wang et al. 2011
	Enhances macrophage phagocytosis of bacteria and efferocytosis of neutrophils	Abdulnour et al. 2015

Mediator	Actions	Reference
RvE1	Reduces neutrophil recruitment, bacterial burden, pro-inflammatory cytokine production and enhances survival; Accelerates resolution of pulmonary inflammation by promoting neutrophil apoptosis	Seki et al. 2010; El Kebir et al. 2012
Viral Lung Infection		
LXA_4	Promotes alternatively activated macrophage phenotype for clearance of infection, accelerates inflammation resolution	Shirey et al. 2014
RvE1	Administered prior to RSV infection promotes pro-resolving alternatively activated macrophage for clearance of infection and accelerates resolution	Shirey et al. 2014
PD1	Inhibits influenza virus replication; Improves pulmonary function and survival	Morita et al. 2013

Abbreviations: LXA_4, lipoxin A_4; LXB_4, lipoxin B_4; RvD1, resolvin D1; RvD2, resolvin D2; RvD3, resolvin D3; RvE1, resolvin E1; PD1, protectin D1; MaR1, maresin 1.

Table 2

Deficient Specialized Pro-Resolving Mediator Biosynthesis in Human Lung Diseases

Mediator	Finding	Reference
Asthma		
LXA_4	Decreased in blood, bronchoalveolar lavage fluid, sputum and exhaled breath condensates in patients with severe asthma	Bhavsar et al. 2010; Celik et al. 2007; Fritscher et al. 2012; Kazani et al. 2013;Levy et al. 2005; Planaguma et al. 2008; Vachier et al. 2005
	Reduced in exhaled breath condensates of children with status asthmaticus	Hasan et al. 2012
	Decreased in children with exercise-induced asthma	Tahan et al. 2008
	Decreased in aspirin-intolerant asthma	Celik et al. 2007; Sanak et al. 2000; Yamaguchi et al. 2011
PD1	Decreased in exhaled breath condensates in uncontrolled asthma	Levy et al. 2007
	Decreased eosinophil production in in severe asthma	Miyata et al. 2013
Chronic Obstructive Pulmonary Disease (COPD)		
LXA_4	Reduced in exhaled breath condensates in moderate to severe COPD	Fritscher et al. 2012
	Reduced relative to serum amyloid A (SAA) during acute exacerbations of COPD	Bonzinovski et al. 2012
LXB_4	Reduced in exhaled breath condensates in moderate to severe COPD patients	Croasdell et al. 2015
RvD1	Reduced in BALF and serum in COPD	Croasdell et al. 2015
Cystic Fibrosis (CF)		
LXA_4	Decreased in airway secretions	Karp et al. 2004; Yang et al. 2012
	Production is compromised by *Pseudomonas aeruginosa*	Flitter et al. 2017
RvE1	Undetectable levels are related to lower lung function	Yang et al. 2012

Abbreviations: LXA_4, lipoxin A_4; LXB_4, lipoxin B_4; RvD1, resolvin D1; RvE1, resolvin E1; PD1, protectin D1.

Table 3

Biological Actions of Specialized Pro-Resolving Mediators in Human Lung Diseases

Mediator	Actions	Reference
Asthma		
LXA_4	Relaxes of bronchoconstricted airways *in vitro* and *in vivo*	Dahlen et al. 1988; Christie et al. 1992
	Enhances natural killer cell-mediated apoptosis of granulocytes	Barnig et al. 2013
	Inhibits IL-13 production by type 2 innate lymphoid cells	Barnig et al. 2013
	Topical 15-epi-LXA_4 relieves dermal inflammation in infants with eczema	Wu et al.2013
n-3 PUFA	High dose supplementation of pregnant women reduces the incidence of persistent wheeze and asthma in their children by one-third	Bisgaard et al. 2016
Chronic Obstructive Pulmonary Disease (COPD)		
RvD1	Suppresses cytokine production from human lung fibroblasts and airway epithelial cells	Hsiao et al. 2013 Hsiao et al. 2014
	Inhibits NF-κB signaling in human airway epithelial cells	
RvD2	Reduces pro-inflammatory cytokine release from cigarette smoke-exposed human alveolar macrophages	Croasdell et al. 2015
RvE1	Attenuates cigarette smoke-induced superoxide production and death in human macrophages	Takamiya et al. 2012
Cystic Fibrosis		
LXA_4	Inhibits IL-8 production by *P. aeruginosa*-exposed human bronchial epithelial cells	Karp et al. 2004
	Levels increase in patients after antibiotic treatment	Chiron et al. 2008
15-epi-LXA_4	BALF levels are positively correlated with lung function	Flitter et al. 2017

Abbreviations: LXA_4, lipoxin A_4; n-3 LCPUFA, n-3 long-chain polyunsaturated fatty acids; RvD1, resolvin D1; RvD2, resolvin D2; RvE1, resolvin E1; 15-epi-LXA_4, 15-epimer of lipoxin A_4.