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Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Towards targeting resolution pathways of airway inflammation in asthma

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ARTICLE INFO

Keywords:

Asthma
Resolution
Lipoxin
Resolvin
Protectin
Maresin

ABSTRACT

Asthma is a chronic disorder characterized by persistent inflammation of the airways with mucosal infiltration of eosinophils, T lymphocytes, and mast cells, and release of proinflammatory cytokines and lipid mediators. The natural resolution of airway inflammation is now recognized as an active host response, with highly coordinated cellular events under the control of endogenous pro-resolving mediators that enable the restoration of tissue homeostasis. Lead members of proresolving mediators are enzymatically derived from essential polyunsaturated fatty acids, including arachidonic acid-derived lipoxins, eicosapentaenoic acid-derived E-series resolvins, and docosahexaenoic acid-derived D-series resolvins, protectins, and maresins. Functionally, these specialized pro-resolving mediators can limit further leukocyte recruitment, induce granulocyte apoptosis, and enhance efferocytosis by macrophages. They can also switch macrophages from classical to alternatively activated cells, promote the return of non-apoptotic cells to lymphatics and blood vessels, and help initiate tissue repair and healing. In this review, we highlight cellular and molecular mechanisms for successful resolution of inflammation, and describe the main specialized pro-resolving mediators that drive these processes. Furthermore, we report recent data suggesting that the pathobiology of severe asthma may result in part from impaired resolution of airway inflammation, including defects in the biosynthesis of these specialized pro-resolving mediators. Finally, we discuss resolution-based therapeutic perspectives.

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Abbreviations: AA, Arachidonic acid; ALX/FPR2, Lipoxin A₄/formyl peptide receptor 2; AnxA1, Annexin A1; ASA, Acetylsalicylic acid; AT, Aspirin-triggered; BHR, Bronchial hyper-reactivity; COX, Cyclooxygenase; DHA, Docosahexaenoic acid; Eos, Eosinophils; EPA, Eicosapentaenoic acid; HEPE, Hydroxyeicosapentaenoic acid; HETE, Hydroperoxyeicosatetraenoic acid; IL, Interleukin; IFN, Interferon; ILC2, Type 2 innate lymphoid cells; LOX, Lipoxygenase; LT, Leukotrienes; LTA₄, Leukotriene A₄; LXA₄, Lipoxin A₄; LXB₄, Lipoxin B₄; Ly, Lymphocyte; MaR1, Maresin 1; NK cells, Natural killer cells; PGD₂, Prostaglandin D₂; PD1, Protectin D₁; PGE₂, Prostaglandin E₂; PLA2, Secretory phospholipase A₂; PMN, Polymorphonuclear cell; PUFA, Polyunsaturated fatty acids; RvD1, Resolvin D₁; RvE1, Resolvin E₁; SPMs, Specialized pro-resolving lipid mediators; Th2, T helper type-2; Th17, T helper type-17.

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<https://doi.org/10.1016/j.pharmthera.2018.01.004>
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Please cite this article as: Barnig, C., et al., Towards targeting resolution pathways of airway inflammation in asthma, *Pharmacology & Therapeutics* (2018), <https://doi.org/10.1016/j.pharmthera.2018.01.004>

1. Introduction

Inflammation is a response initiated by the host that has developed throughout evolution in response to tissue insult or injury (Medzhitov, 2008). It is initiated within minutes of recognition of a danger signal with the ultimate purpose to restore tissue integrity and homeostasis.

The acute inflammatory response is a highly coordinated sequence of events involving a large number of molecular, cellular and physiological interplays (Nathan, 2002). Early events are controlled by several families of chemokines, cytokines and pro-inflammatory mediators (including lipid mediators such as prostaglandins and leukotrienes) produced by resident cells in the injured tissue. They act in a coordinated fashion to drive the initiation of the inflammatory reaction with edema from leakage-permeability changes followed by a rapid influx of granulocytes (e.g. neutrophils) from blood to the inflammatory site, and by a self-amplifying network of pro-inflammatory pathways, which perpetuate leukocyte recruitment and activation (Larsen & Henson, 1983). In otherwise healthy tissues, the inflammatory response is programmed to stay within limits, both spatial and temporal, resolving and returning the injured tissues to the pre-inflamed state. If the process of resolution fails, inflammation is perpetuated, resulting into chronicity with tissue injury, remodelling and subsequent fibrosis and loss of tissue function (Serhan, 2017). Persistent and non-resolving inflammation has emerged as a critical process in the pathogenesis of numerous chronic diseases, including asthma where chronic airway inflammation is central to the pathogenesis of the disease (Holgate, 2012).

Until the beginning of this century, acute inflammation was thought to resolve passively, involving a decreased expression of cytokines, the dilution of chemokine gradients over time, and the natural catabolism of pro-inflammatory mediators; together explaining why leukocytes stop migrating from blood into tissues. However, investigations in the past decade have identified critical molecular and cellular processes that are specifically engaged in the inflammatory response to actively promote resolution, leading to a new paradigm in our understanding of the host mechanisms for cessation of the inflammatory response (Serhan, 2017). Elucidating these mechanisms of resolution of the inflammatory process is therefore of great interest, since it can provide new windows to understand disease pathogenesis and design rationale therapeutic approaches to augment host resolution mechanisms (Fig. 1).

In this review, we discuss the recent discoveries in resolution pathways involved in asthmatic inflammation with a focus on the role of specialized pro-resolving mediators (SPMs) derived from polyunsaturated fatty acids (PUFAs) and their potential therapeutic applications.

2. Airway inflammation in asthma

Asthma is a very common inflammatory disorder of the conducting airways affecting 300 million people worldwide due to bronchial hyper-reactivity (BHR), subsequent airway smooth muscle contraction, airway remodelling with edema, subepithelial fibrosis and mucus hypersecretion leading to airflow limitation and breathing difficulties (Busse & Lemanske, 2001; Lambrecht & Hammad, 2015).

Besides episodes of acute inflammation in response to various stimuli, such as allergen inhalation, exposure to micro-environmental pollutants or viral infection, an underlying chronic airway inflammation is often found, even in patients with infrequent or recent-onset asthma symptoms (Bousquet, Jeffery, Busse, Johnson, & Vignola, 2000). The airway inflammation in chronic asthma is mediated in many cases through ongoing type 2 responses with infiltration of activated mast cells, dendritic cells (DCs) and T helper type-2 (Th2) cells into the bronchial mucosa, that release pro-inflammatory mediators (e.g. interleukin (IL)-5, IL-13, prostaglandins, leukotrienes, ...) and cause eosinophil (Eos) infiltration (Lloyd & Hessel, 2010), a hallmark of asthmatic inflammation (Fig. 2).

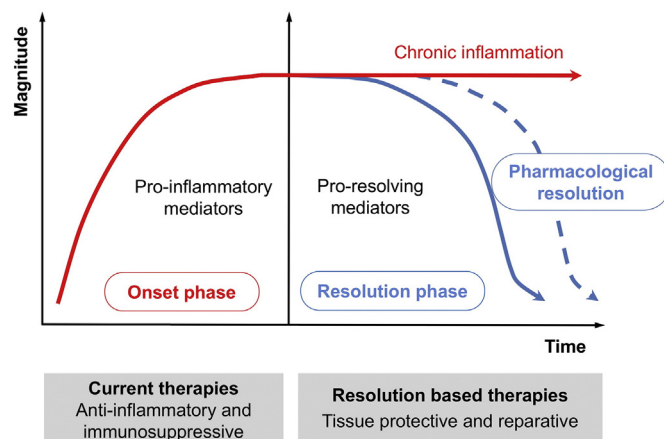


Fig. 1. Dynamics of the inflammatory response. The acute inflammatory response is a highly coordinated sequence of events characterized i) by an onset phase coordinated by several families of chemokines, cytokines and pro-inflammatory mediators that is followed ii) in health by an active resolution phase brought about by the engagement of specific cellular mechanisms under the control of several pro-resolving mediators to promote resolution of the tissue inflammation as well as healing and repair. A failure in proresolving pathways can extend in time the actions of proinflammatory mechanisms resulting in prolonged or chronic inflammation. Current therapeutic agents are predominantly anti-inflammatory in their action with mixed success and most of them are also immunosuppressive. As discussed in this review, elucidating the mechanisms of resolution of the inflammatory process is of relevance, since it can give rise to new therapeutic approaches by exploiting the intrinsic tissue repair systems.

In addition, a role of type 2 innate lymphoid cells (ILC2) was recently reported (Barnig et al., 2013; Lambrecht & Hammad, 2015). Indeed, ILC2 play crucial roles in the initiation and propagation of type 2 inflammatory responses in allergic asthma models. They are directly activated by epithelial cell-derived cytokines (e.g. IL-25, IL-33, thymic stromal lymphopoietin) and mast-cell derived prostaglandin D₂ (PGD₂) and can independent of adaptive immunity induce bronchial hyperreactivity through the production of IL-13 and airway eosinophilia through the production of IL-5 (Barlow et al., 2012; Chang et al., 2011; Kim et al., 2012). During the allergic asthmatic inflammatory response in murine asthma models, ILC2 can also be activated by vasoactive intestinal peptide released by nodose ganglion neurons through the activation of nociceptive transient receptor potential (TRP) channels (Talbot et al., 2015), as complex interplays between nociceptors and immune cells in the asthmatic inflammatory response (Baker et al., 2016; Grace, Baxter, Dubuis, Birrell, & Belvisi, 2014).

Asthma exacerbations are notable for a neutrophil (PMN)-enriched inflammatory response, which in some cases can also be the principal cellular infiltrate in chronic asthma (Duvall et al., 2017; Li et al., 2015; Peters et al., 2014; Simpson et al., 2016). In this neutrophil-predominant disease, Th17 cells are mainly involved, via IL-17 production promoting neutrophil recruitment (Cosmi, Liotta, Maggi, Romagnani, & Annunziato, 2011).

Activated structural cells (e.g. airway epithelial and smooth muscle cells) together with inflammatory cells perpetuate the chronic inflammation by the secretion of a vast array of pro-inflammatory mediators, including eicosanoids, cytokines, chemokines, growth factors which contribute to the symptoms and BHR observed in asthma patients (Djukanovic et al., 1990; O'Byrne & Postma, 1999).

Along with airway inflammation, disruption of the respiratory epithelial tight junctions responsible for impaired epithelial barrier function is observed (Holgate, 2007; Xiao et al., 2011). Other structural changes are characteristic of the airways of asthma patients, termed 'airway remodelling'. These changes include sub-epithelial fibrosis, thickening of airway smooth muscle, increased number of airway wall blood vessels, increased number of goblet cells in the airway epithelium, and increased size of sub-mucosal glands. Some of these changes have been related to the severity of the disease and may result in irreversible

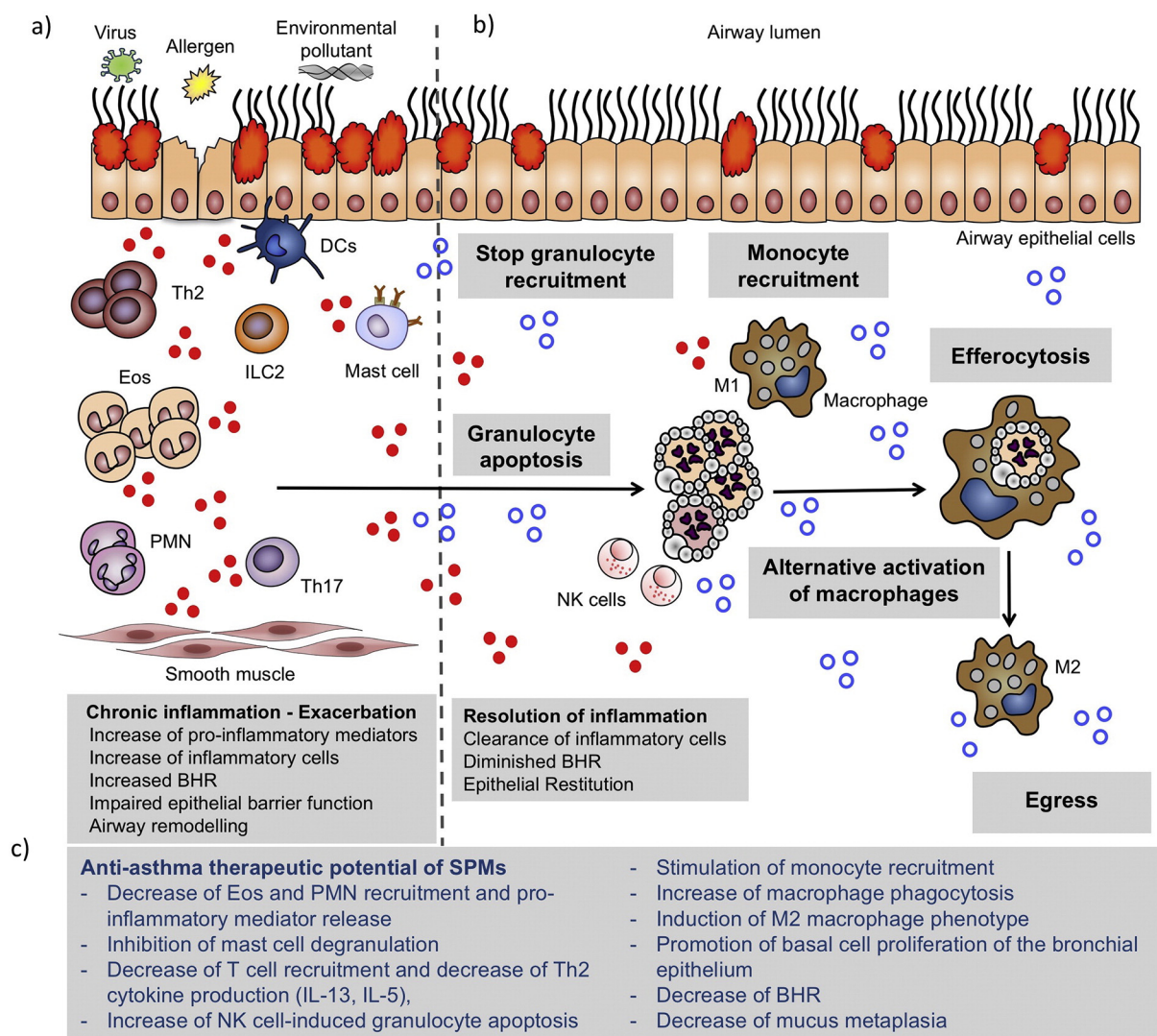


Fig. 2. Airway inflammation in asthma and defects in key steps of resolution. a) In asthma, inflammation of the airways is one of the central abnormalities, driven by a multitude of underlying disease processes in response to a variety of stimuli, such as allergen inhalation, exposure to micro-environmental pollutants or viral infection. Many inflammatory cells of the innate and adaptive immune systems act along with activated resident structural cells, such as airway epithelial cells and airway smooth muscle cells, to perpetuate inflammation by the secretion of a vast array of pro-inflammatory mediators (closed red circles) (e.g. eicosanoids (prostaglandins, leukotrienes), cytokines (IL-5, IL-4, IL-13, IL-17...), chemokines, growth factors and proteases). This results in BHR, mucus overproduction, epithelial barrier dysfunction and airway wall remodeling. b) The resolution of airway inflammation is now recognized as an active process brought about by the biosynthesis of active endogenous anti-inflammatory and pro-resolving mediators released from various cell types (open blue circles), which act on key cellular events of inflammation to promote the return to homeostasis. In the first phase of resolution of airway inflammation, pro-inflammatory signaling is terminated and granulocyte recruitment is stopped. In the second phase, monocytes are recruited and programmed cell death or apoptosis of the inflammatory granulocytes is initiated through death signals in part mediated via NK cells. In the third phase, the apoptotic cells are phagocytosed and cleared by the macrophages (efferocytosis) that switch from a classically activated phenotype (M1) to an alternatively activated (M2) pro-resolving phenotype and initiate repair and normalization of tissue architecture and function. They subsequently migrate to the draining blood or lymph vessels (egress). Increasing evidence from translational data indicate that persistent uncontrolled inflammation in asthma might result not just from an increased or repetitive exposure to provocative stimuli leading to excessive airway inflammation but also from defective engagement of pro-resolving pathways including decreased production of pro-resolving mediators, disruption of granulocyte apoptosis, failure of airway macrophages to efficiently clear apoptotic cells by phagocytosis, and dysregulated wound-repair (Section 3.3 and Table 4). c) Lipoxins, resolvins, protectins and maresins are specialized pro-resolving mediators (SPMs) generated from polyunsaturated fatty acids (PUFAs) that have many cell-type specific actions *in vitro* and biologic activities in murine asthma models with anti-asthma therapeutic potential. Details are precised in Section 4.3 and Tables 2 and 3. BHR: bronchial hyper-reactivity; DCs: dendritic cell; Eos: eosinophil; ILC2: type 2 innate lymphoid cell; M1: classically activated macrophage; M2: alternatively activated macrophage; NK cell: natural killer cell; PMN: neutrophil; Th2: T helper type-2 lymphocyte; Th17: T helper type-17 lymphocyte; Treg: T regulatory cells; SPMs, specialized pro-resolving mediators. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

narrowing of the airways in patients with long-standing asthma (Chung et al., 2014).

3. Principles of resolution of inflammation

Resolution of inflammation (known as catabasis) is the reduction or removal of leukocytes and debris from inflamed sites enabling the return to homeostasis. Several cellular mechanisms enable the repair of inflamed or injured tissues and restore homeostasis, and many of

those processes are promoted by a large, growing class of molecules called specialized pro-resolving mediators (Levy & Serhan, 2014) (Gilroy, Lawrence, Perretti, & Rossi, 2004).

More specifically in asthma inflammation, it requires the clearance of inflammatory leukocytes within the lung, together with the restoration of epithelial barrier integrity and function and dampening of BHR (Busse & Lemanske, 2001). A schematic representation of the key steps of the resolution of airway inflammation in asthma is depicted on Fig. 2.

3.1. Key cellular steps

A critical requirement for the inflammatory response to switch off is the cessation of pro-inflammatory mediator synthesis, normalization of chemokine gradients that will limit further granulocyte recruitment, followed by the recruitment of monocytes that will differentiate into macrophages (Henson, 2005).

Local granulocytes are cleared by programmed cell death (apoptosis) with subsequent phagocytosis by the surrounding macrophages (efferocytosis). Apoptosis of eosinophils in the airways and their uptake by phagocytes is considered a predominant cellular mechanism of resolution of inflammation in asthma patients, as their delayed clearance could induce secondary necrosis and subsequent release of toxic cellular contents leading to tissue damage and persistence of inflammation (Savill, 1998; Savill & Fadok, 2000; Vandivier, Henson, & Douglas, 2006; Woolley et al., 1996). Notably, in a murine model of allergic asthma, lung eosinophils and antigen-specific CD4⁺ T cells are cleared concomitantly to the occurrence of increased numbers of local natural killer (NK) cells (Haworth, Cernadas, & Levy, 2011). A potential interaction between eosinophils and NK cells during the resolution phase of asthma has been further determined in human asthma, where apoptosis of eosinophils can be induced through direct contact with NK cells (Awad et al., 2014; Barnig et al., 2013). NK cells contribute also to the resolution of asthmatic inflammation through cytotoxic mechanisms (Duvall et al., 2017).

Phagocytosis of apoptotic leukocytes by macrophages prompts a switch from a pro- (M1) to an anti-inflammatory (M2) macrophage phenotype, able to release anti-inflammatory cytokines, growth factors and pro-resolving mediators (Dalli & Serhan, 2012; Wynn, Chawla, & Pollard, 2013). Once phagocytosis is complete, macrophages can leave the inflamed site *via* blood or lymph.

T regulatory (Treg) cells, as well as myeloid-derived suppressor cells (MDSCs) have more recently emerged as additional players in the resolution of inflammation by stimulating apoptosis and enhancing the efferocytosis capacity of macrophages. They may link innate and adaptive immune responses during inflammation (D'Alessio et al., 2009; Huang et al., 2006; Newson et al., 2014; Poe et al., 2013). Their role in the chronicity of airway inflammation is not yet completely understood but Treg cells have been recently shown to inhibit ILC2 activation and restrain allergic lung inflammation in a murine model (Krishnamoorthy et al., 2015).

3.2. Pro-resolving mediators

During the inflammatory response, several endogenous anti-inflammatory and pro-resolving mediators are produced in a coordinated temporal and spatial manner, in order to restrain and resolve inflammation. Anti-inflammatory mediators dampen inflammation by inhibiting intracellular pro-inflammatory signalling pathways, reducing chemotaxis and limiting migration of granulocytes into the tissues and can therefore display immunosuppressive actions.

Distinct from anti-inflammatory mediators, pro-resolving mediators are by definition not immunosuppressive but rather tissue protective and reparative (Fig. 1). They are able to enhance the host immune response by promoting key cellular steps of resolution of inflammation. Indeed, these molecules stimulate non-phlogistic recruitment of monocytes (that is, without elaborating pro-inflammatory mediators), induce granulocyte apoptosis, enhance macrophage phagocytosis of apoptotic cells, switch macrophages from classical to alternatively activated cells, promote the return of non-apoptotic cells to the lymphatics and blood vessels, and stimulate tissue regeneration to reconstitute barrier integrity (Levy & Serhan, 2014; Serhan, Chiang, & Van Dyke, 2008) (Table 1).

The host-protective actions of SPMs are further underlined in infection, where they promote host defence in preclinical models of viral and bacterial lung infection, including increased production of antimicrobial peptides and enhanced macrophage phagocytosis of pathogens

Table 1

Actions of pro-resolving mediators. Pro-resolving mediators are defined by fulfilling fundamental criteria essential for the timely resolution of inflammation.

1. Limit or cease the recruitment of further leukocytes
2. Counter-regulate chemokines and cytokines
3. Promote the non-phlogistic recruitment of monocytes
4. Induce granulocyte apoptosis
5. Enhance the phagocytosis of apoptotic cells by macrophages
6. Switch macrophages from classical to alternatively activated cells
7. Promote the return of non-apoptotic cells to blood or the lymphatics
8. Initiate tissue repair mechanism and healing

leading to enhanced pathogen clearance (Chiang et al., 2012; Morita et al., 2013; Seki et al., 2010; Spite et al., 2009).

Several pro-resolving mediators have been identified, diverse in nature and displaying some overlapping functions, emphasizing the importance of controlling the inflammatory response. These pro-resolving mediators include lipid mediators known as SPMs (lipoxins, resolvins, protectins, maresins), proteins and peptides like annexin A1 (Perretti & D'Acquisto, 2009), galectins (Ahmed, Kaneva, Pitzalis, Cooper, & Perretti, 2014), chemerin (Mariani & Roncucci, 2015), adrenocorticotrophic hormone (Montero-Melendez, 2015), gaseous mediators (e.g. hydrogen sulphide and carbon monoxide) (Wallace, Ianaro, Flannigan, & Cirino, 2015), a purine (adenosine) (Hasko & Cronstein, 2013), as well as neuromediators (like acetylcholine or neuropeptides) (Mirakaj, Dalli, Granja, Rosenberger, & Serhan, 2014; Pavlov & Tracey, 2012).

3.3. Defective resolution of inflammation in asthma

There is increasing evidence from translational data that chronic and uncontrolled inflammation in asthma might result not just from an increased or repetitive exposure to provocative stimuli leading to excess airway inflammation but also from uncontrolled and insufficient engagement of counter-regulatory, pro-resolving pathways.

Indeed, decreased levels of pro-resolving lipid mediators together with a defect in the expression of the related biosynthetic genes and receptors are linked to severe and uncontrolled asthma (Kazani et al., 2013; Levy et al., 2005; Planaguma et al., 2008) (for more details see Section 4.3.3).

The pathophysiology of chronic asthma involves a disruption of leukocyte apoptosis, in particular eosinophils (Duncan, Lawrie, Blaylock, Douglas, & Walsh, 2003), together with a failure of airway macrophages to efficiently clear apoptotic cells by phagocytosis, which may correlate with asthma severity (Fernandez-Boyanapalli et al., 2013; Fitzpatrick, Holguin, Teague, & Brown, 2008; Lamb et al., 2005; Simpson et al., 2013; Vandivier et al., 2006). Defects in efferocytosis might contribute to perpetuation of inflammation in patients with asthma, not only through a secondary cell necrosis, but also through reduced release of regulatory and pro-resolving mediators that are normally produced upon recognition of apoptotic cells by airway macrophages (Huynh et al., 2005).

Furthermore, speculation from microarray studies on epithelial brushings from a range of asthmatics of different types of severity suggest insufficient return to tissue homeostasis with dysregulated expression of wound-repair related genes in those with more severe disease (Modena et al., 2016).

4. Specialized pro-resolving lipid mediators

In the past two decades, experimental models of acute inflammation that are self-limiting and naturally resolve have led to the identification of a novel family of specialized pro-resolving mediators (SPM) generated from polyunsaturated fatty acids (PUFAs) including lipoxins, resolvins, protectins and maresins (Serhan et al., 2008).

SPMs are generated *via* lipoxygenase (LOX)-catalyzed reactions. Lipoxins are the lead members of the SPM family. While structurally

and functionally distinct from prostaglandins and leukotrienes, lipoxins are also products of arachidonic acid (AA, C20:4n – 6) metabolism. In addition to AA, the omega-3 PUFAs eicosapentaenoic acid (EPA, C20:5n – 3) and docosahexaenoic acid (DHA, C22:6n – 3) can also be enzymatically converted by LOX-catalyzed reactions to SPMs, including resolvins, protectins and maresins (Fig. 3).

During the time-course of acute inflammation, SPM biosynthesis in resolution exudates is initiated by lipid-mediator class switching, in which early pro-inflammatory mediators of the upstroke of acute inflammation, such as prostaglandins and leukotrienes, are pivotal to activating the biosynthetic machinery for the later conversion of PUFA to SPMs (Levy, Clish, Schmidt, Gronert, & Serhan, 2001).

Many of the SPMs are produced during cell–cell interaction between leukocytes and structural cells that express the required biosynthetic enzymes in a compartmentalised manner with intermediate metabolites shared between the cells in a bidirectional manner (Fiore & Serhan, 1990).

These bioactive lipids display potencies in the nanomolar range, and signal through cognate receptors with cell type-specific actions.

4.1. Lipoxins (LXs)

Lipoxin A₄ (LXA₄) was the first PUFA-derived pro-resolving mediator identified (Serhan, Hamberg, & Samuelsson, 1984).

4.1.1. Biosynthesis

Lipoxins (LXs) are downstream products of the omega-6 arachidonic acid (AA) (C20:4n – 6) incorporated into phospholipids in cell membranes. Upon cell activation, specific phospholipase A₂ (PLA₂) enzymes liberate AA from the sn-2 fatty acyl bond of these phospholipids (Serhan et al., 1984). AA can be enzymatically converted to LXs, or to PGs and LTs following the biosynthetic pathways described below (Samuelsson, Dahlen, Lindgren, Rouzer, & Serhan, 1987) (see Fig. 3).

The term lipoxin derives from “lipoxygenase interaction products”. Because lipoxin biosynthetic lipoxygenases are predominantly compartmentalized in distinct cell types, lipoxins are principally generated at sites of multicellular interactions, such as during inflammation, through transcellular interaction between distinct cell types with biosynthetic intermediate metabolites passing between them (Fiore & Serhan, 1990; Serhan & Sheppard, 1990).

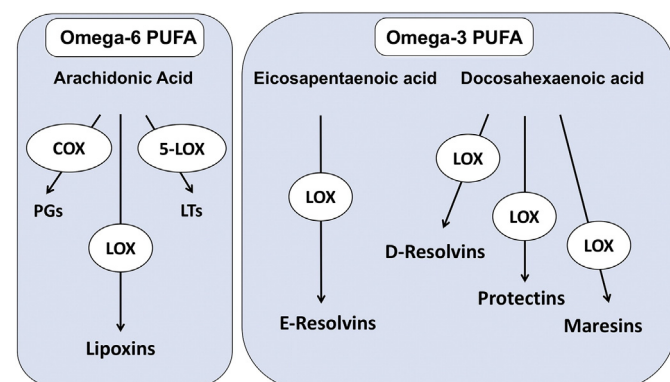


Fig. 3. Formation of bioactive lipid mediators. Specific pro-resolving lipid mediators (SPMs) are enzymatically derived in a spatio-temporally regulated manner during the inflammatory response via different lipoxygenase (LOX) pathways from polyunsaturated fatty acid (PUFA). PUFA are either released enzymatically by phospholipase A₂ (PLA₂) from cell membranes or delivered with edema fluid from plasma to inflammatory sites. SPMs include omega-6 PUFA arachidonic acid (AA) (C20:4n – 6) derived lipoxins, as well as omega-3 PUFA eicosapentaenoic acid (C20:5n – 3) and docosahexaenoic acid (C22:6n – 3) derived resolvins, protectins and maresins. AA also forms a range of pro-inflammatory mediators, such as prostaglandins (PGs) via cyclooxygenase (COX)-2, and the leukotrienes (LTs) via 5-LOX actions.

In airway inflammation, a major pathway of LX formation is initiated by 15-LOX, expressed predominantly by bronchial epithelial cells in inflamed lung (Hunter, Finkbeiner, Nadel, Goetzl, & Holtzman, 1985; Shannon, Chanez, Bousquet, & Holtzman, 1993) and to a lesser degree by cytokine-exposed lung macrophages (Levy et al., 1993; Profita et al., 2000) (Fig. 4). Human eosinophils express abundant 15-LOX, and can also participate in lipoxin production (Feltenmark et al., 2008; Miyata et al., 2013; Serhan, Hirsch, Palmblad, & Samuelsson, 1987). 15-LOX converts AA to an unstable intermediate 15(S)-hydroperoxyeicosatetraenoic acid (15(S)-HPETE), which can serve as a substrate for 5-LOX for conversion to LXA₄ (5S,6R,15S-trihydroxy-7,9,11,13-eicosatetraenoic acid) or LXB₄ (5S,14R,15S-trihydroxy-6,8,10,12-eicosatetraenoic acid) (Levy et al., 1993; Serhan et al., 1984). 5-LOX expression in the human inflamed lung is mainly present in leukocytes (Levy et al., 2001, 2002).

A second pathway for LX production involves interactions between neutrophils and platelets within the vasculature. Neutrophil–platelet aggregates form during inflammatory responses to promote secondary capture of neutrophils into inflamed target tissues. Of interest, neutrophil 5-LOX can convert AA to LTA₄ that can be exported to platelets for conversion by platelet 12-LOX to LXA₄ or LXB₄ (Edenius, Haeggstrom, & Lindgren, 1988; Edenius, Heidvall, & Lindgren, 1988; Fiore & Serhan, 1990; Serhan & Sheppard, 1990) (Fig. 4).

In addition, several pharmacological interventions can induce the formation of lipoxin epimers (Fig. 4). Acetylsalicylic acid (ASA) alters the catalytic properties of cyclo-oxygenase (COX)-2 to inhibit PG biosynthesis, yet promote the conversion of AA to 15(R)-HETE, which can serve as a transcellular substrate for 5-LOX mediated conversion to 15-epimeric versions of lipoxins (also known as aspirin-triggered-lipoxins (ATL)) (Fig. 4) (Claria & Serhan, 1995) (Fig. 4). Similar to ASA, statins can also induce 15-epimer-lipoxin production, including in the airways, via the S-nitrosylation of COX-2 (Birnbaum et al., 2006; Planaguma et al., 2010). Of note, 15(R)-HETE can also be produced through the action of the cytochrome P450 enzymes (Claria, Lee, & Serhan, 1996) (Fig. 4).

Lipoxins are found in low concentration during the initiation phase of acute inflammation, but their biosynthesis is significantly increased during lipid-mediator class switching, where early PGE₂ and PGD₂ activate the production of lipoxins by switching the predominant LOX activity in leucocytes from 5-LOX to 15-LOX (Haworth, Cernadas, Yang, Serhan, & Levy, 2008; Levy et al., 2001; Ortega-Gomez, Perretti, & Soehnlein, 2013). Indeed, growing evidence suggests that early pro-inflammatory events regulate the biosynthesis of SPM to promote the resolution of inflammation.

LXs act locally and are rapidly inactivated at sites of inflammation by metabolic enzymes (*i.e.* 15-hydroxyprostaglandin dehydrogenase (15-PGDH) and 15-oxoprostaglandin 13-reductase) shared with other eicosanoids including prostaglandins and leukotrienes (Clish, Levy, Chiang, Tai, & Serhan, 2000). LX metabolism is stereospecific, so 15-epi-LXs are metabolized less efficiently, which increases the biological half-life approximately 2-fold (Claria & Serhan, 1995; Serhan et al., 1995).

4.1.2. Receptors

LXA₄ is an agonist to the lipoxin A₄/formyl peptide type 2 receptor (ALX/FPR2), a 7-transmembrane G protein-coupled receptor belonging to the N-formyl peptide receptor family (Chiang et al., 2006; Fiore, Maddox, Perez, & Serhan, 1994). In PMN, ALX/FPR2 signals in part via polyisoprenyl phosphate remodeling (presqualene diphosphate to presqualene monophosphate; Levy et al., 1999), as well as via inhibition of leukocyte specific protein (LSP)-1 phosphorylation, a downstream regulator of p38-MAPK cascade (Ohira et al., 2004). 15-epi-LXA₄ retains essentially identical binding affinity to ALX/FPR2 (Takano et al., 1997). The ALX/FPR2 receptor displays diverse ligand affinities that extend beyond interactions with LXA₄ and 15-epi-LXA₄. Indeed, ALX/FPR2 can interact with over 30 ligands with various affinities, and has been

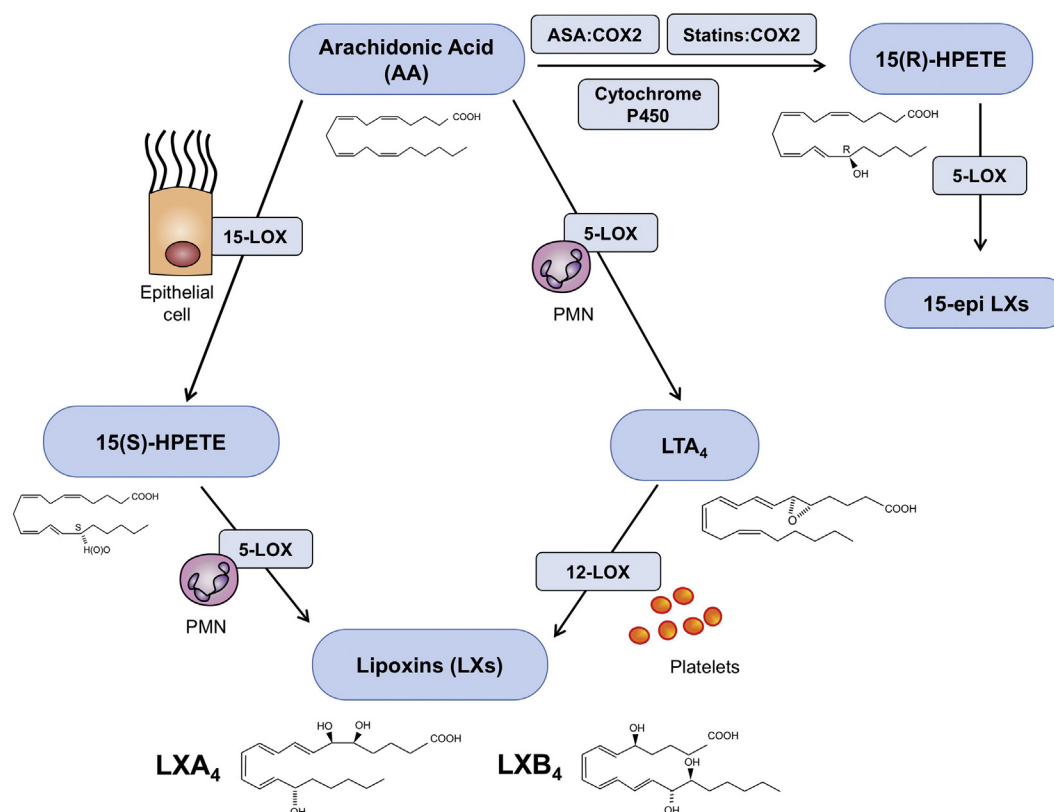


Fig. 4. Main biosynthetic pathways of lipoxins. Lipoxins are downstream products of AA (20:4n – 6). As circulating leukocytes traffic into the lung, their 5-LOX can collaborate with airway epithelial 15-LOX to generate lipoxins during transcellular interactions. Biosynthetic intermediates derived via 15-LOX from AA, such as 15(S)-hydroperoxy-eicosatetraenoic acid (15(S)-HpETE) can serve as stereospecific substrates for conversion to lipoxins by 5-LOX. Another pathway involves platelet-leukocyte interactions. Leukocyte 5-LOX converts AA to LTA₄. When platelets are adherent to neutrophils, their 12-LOX converts LTA₄ to LXA₄ and LXB₄. Additionally, biosynthesis can occur either by airway cytochrome P450, aspirin-acetylated COX-2 or statin-S-nitrosylated COX-2 to generate 15-epi-lipoxins during cell-cell interactions. AA: arachidonic acid; COX: cyclo-oxygenase; LOX: lipoxygenase; LT: leukotriene; LX: lipoxin.

identified as the first receptor to engage both bioactive lipids and peptides/proteins, including annexin A₁ (Perretti et al., 2002). Thereby, ALX/FPR2 ligands can exert opposing biological actions in a ligand specific manner to either promote inflammation or its resolution. ALX/FPR2 can form homo- as well as heterodimers, and these complexes dictate pro-inflammatory or pro-resolution responses to agonists (Cooray et al., 2013).

ALX/FPR2 demonstrates wide tissue distribution and is expressed on human leukocytes, including neutrophils, eosinophils, monocyte-macrophages, T cells, human NK cells and ILC2, as well as on tissue resident cells, such as airway epithelial cells and fibroblasts (Barnig et al., 2013; Bonnans, Fukunaga, Levy, & Levy, 2006; Chiang et al., 2006; Fiore et al., 1994; Maddox et al., 1997; Murphy et al., 1992). Orthologs of the ALX receptor are expressed in mice (Takano et al., 1997) and rats (Chiang, Takano, Arita, Watanabe, & Serhan, 2003) with preserved structure and function.

ALX/FPR2 receptor expression is regulated by local inflammatory mediators (Bonnans et al., 2006; Levy et al., 2002). Cytokines for instance, including IL-13 and IFN- γ can induce ALX/FPR2 expression by epithelial cells *in vitro* (Gronert, Gewirtz, Madara, & Serhan, 1998). Lung ALX/FPR2 expression is also induced *in vivo* in a murine model of allergic airway inflammation (Levy et al., 2002).

In addition to signaling through ALX/FPR2, LXA₄ can act as an antagonist to LTD₄ binding to CysLT₁ receptors (Gronert, Martinsson-Niskanen, Ravasi, Chiang, & Serhan, 2001). The receptor for LXB₄ has yet to be identified.

4.2. DHA- and EPA-derived pro-resolving mediators

SPM are also products of omega-3 PUFA metabolism, including docosahexaenoic acid (DHA; 22:6n – 3) and eicosapentaenoic (EPA;

20:5n – 3). These SPM include DHA-derived D-series resolvins (RvD1–6) (D nomenclature derived from DHA), neuroprotectin/protectins (NPD1/PD1), and maresins (MaR1–2) and EPA-derived E-series resolvins (RvE1–3) (E nomenclature derived from EPA).

DHA and EPA in plasma can be delivered from the vasculature to the inflammatory site in edema within minutes after the initial injury (Kasuga et al., 2008). These PUFAs in the inflammatory exudates are available for subsequent enzymatic conversion to SPM. DHA and EPA can also be released from cell membranes upon cell activation through the activity of a selective secretory PLA₂ isoform (Murakami, Taketomi, Sato, & Yamamoto, 2011).

Similar to lipoxins, DHA- and EPA-derived SPMs are produced via LOX-catalyzed reactions during transcellular interactions, and up-regulation of epimeric SPM production by aspirin has been reported (Serhan, Gotlinger, Hong, & Arita, 2004).

4.2.1. D-series resolvins, protectins and maresins

The main biosynthetic pathways for conversion of DHA to the D-series resolvins, protectins, and maresins are illustrated in Fig. 5.

4.2.1.1. D-series resolvins. During airway inflammation, epithelial cell 15-LOX can convert DHA to 17(S)-hydroperoxy-DHA, which can be subsequently converted by neutrophil 5-LOX via epoxide-containing biosynthetic intermediates into D-series resolvins (RvD1–6) (Duvall & Levy, 2016; Hong, Gronert, Devchand, Moussignac, & Serhan, 2003) (Fig. 5).

In the presence of aspirin, DHA can be converted in endothelial cells through aspirin-acetylated COX2 and 5-LOX activities to generate aspirin-triggered 17(R)-hydroperoxy-DHA that can be further transformed to epoxide intermediates for subsequent conversion to 17-epimer RvD1–6 (Marcheselli et al., 2003; Serhan et al., 2002) (Fig. 5).

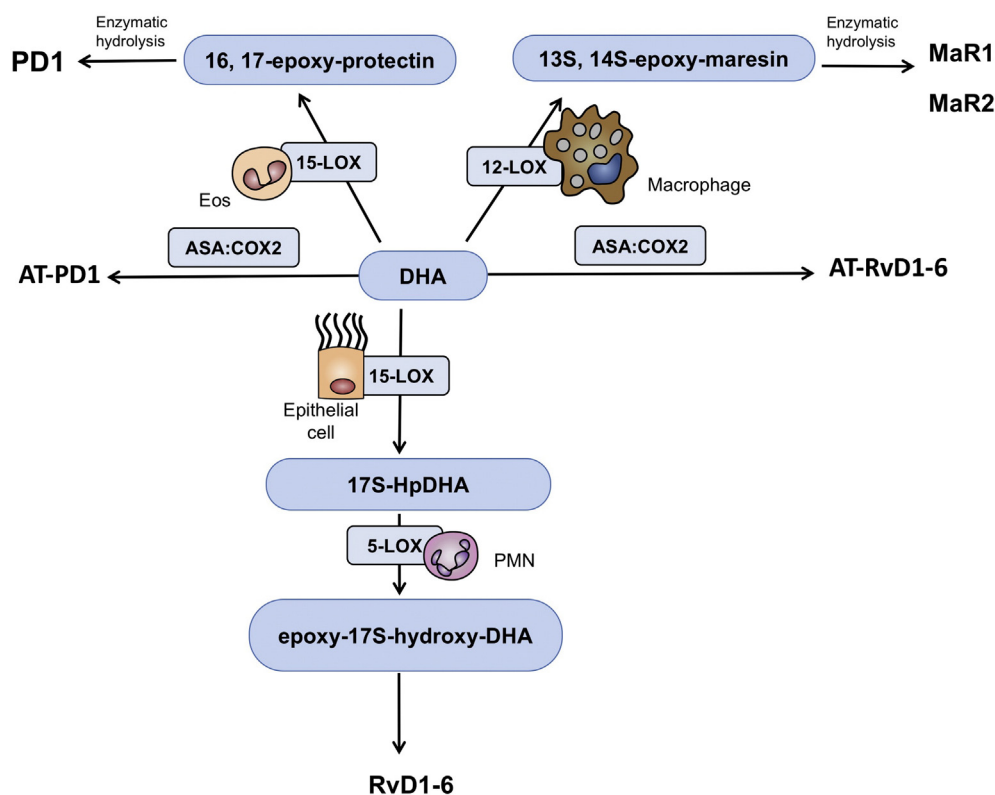


Fig. 5. Biosynthetic pathways for conversion of DHA to the D-series resolvins, protectins, and maresins. DHA is enzymatically converted to 17S-hydroperoxy-DHA intermediate (17-HpDHA) by epithelial 15-LOX which is then further converted by neutrophil derived 5-LOX to epoxide intermediates that are transformed to the D-series resolvins, RvD1 through RvD6. DHA is also converted via 12-LOX in macrophages to a 13S,14S-epoxy-maresin intermediate and then through enzymatic hydrolysis to MaR family members MaR1 and MaR2. DHA can also be converted via eosinophil 15-LOX into a 16,17-epoxy-protectin intermediate which is converted to NPD1/DP1. Low-dose aspirin triggers the 17R and 18R/S epimers of the Rvs (AT-Rvs) and 17R-epimer protectins (AT-PD1).

RvD₁ is a high affinity ligand for the ALX/FPR2 receptor (like LXA₄), implicating this receptor as an integral component of pro-resolution pathways. In addition, RvD₁, its aspirin triggered epimer AT-RvD₁, as well as RvD₃ and RvD₅ can all bind the GPR32 receptor (now known as DRV1, the D-series Resolvin receptor 1 or RvD1 receptor) expressed on human neutrophils, lymphocytes, monocyte-macrophages, as well as in vascular tissues (vascular smooth muscle cells and endothelial cells) (Chiang et al., 2012; Dalli et al., 2013; Krishnamoorthy et al., 2010; Krishnamoorthy, Recchiuti, Chiang, Fredman, & Serhan, 2012; Miyahara et al., 2013; Sun et al., 2007). RvD₁ interacts with DRV₁ during homeostasis, and with ALX/FPR2 during the resolution phase of inflammation (Krishnamoorthy et al., 2012). RvD₂ binds to and signals through GPR18 receptor (now known as DRV2, the RvD2 receptor) expressed on human and murine neutrophils, monocytes and macrophages (Chiang, Dalli, Colas, & Serhan, 2015). The molecular identity of the RvD₄ and RvD₆ cognate receptors is still to be determined.

4.2.1.2. Protectins. Protectins (also known as neuroprotectins in neuronal tissues) are generated via a 15-LOX-dependent manner which catalyses the conversion of DHA to protectin D1 (PD1) via an 16,17-epoxy-protectin intermediate (Hong et al., 2005; Serhan et al., 2006). PD1 is an anti-inflammatory and pro-resolving molecule that is synthesized by 15-LOX-expressing cells, such as human eosinophils (Miyata et al., 2013; Yamada et al., 2011). PD1 specific receptors remain to be identified. Epimeric protectins can also be generated in the presence of aspirin (AT-protectins) (Marcheselli et al., 2003) (Fig. 5).

4.2.1.3. Maresins. Maresins are a third major family of DHA-derived SPMs. Maresins (MaR1 and MaR2) are produced in tissues by macrophages via the actions of 12-LOX, through a 13,14-epoxide intermediate (Dalli et al., 2013; Serhan et al., 2009). MaR1 can also be generated at

sites of vascular inflammation during human platelet–neutrophil interactions via platelet 12-LOX conversion of DHA to 13S,14S-epoxy-maresin, followed by neutrophil conversion to MaR1 (Abdulnour et al., 2014) (Fig. 5). The receptors for maresins have yet to be molecularly characterized.

4.2.2. E-series resolvins

Biosynthesis of E-series resolvins occurs from EPA in vascular endothelial cells through a reaction initiated by acetylated COX2 or CYP450 enzymes (Fig. 6).

Endothelial cells expressing COX2, when exposed to aspirin, will convert EPA to 18R-HEPE that can be further transformed via neutrophil-derived 5-LOX to RvE2 (15S,18R-dihydroxy-hydroxy eicosapentaenoic (EPE) acid) (Arita, Bianchini, et al., 2005; Arita, Yoshida, et al., 2005; Ogawa et al., 2009; Oh et al., 2012; Oh, Pillai, Recchiuti, Yang, & Serhan, 2011; Tjonahen et al., 2006) (Fig. 6). Alternatively, the 18R-HEPE intermediate can be converted to a 5,6-epoxy fatty acid in human PMN by 5-LOX, and eventually to RvE1 by subsequent enzymatic hydrolysis (Arita, Bianchini, et al., 2005; Oh et al., 2011; Serhan et al., 2000). In the absence of aspirin, RvE1 biosynthesis can be initiated through CYP450 enzymatic conversion of EPA (Serhan et al., 2000).

RvE3 is distinct from the other E-series resolvins in its biosynthesis, as it is generated directly from 18R-HEPE via the action of 15-LOX in eosinophils rather than neutrophil 5-LOX (Isobe et al., 2012).

RvE1 and RvE2 are agonists at the chemokine-like receptor 1 (CMKLR1; also known as ChemR23 and recently labeled E-series resolvin (ERV) receptor) (Arita, Bianchini, et al., 2005). This receptor is widely expressed in the lung by both leukocytes and structural cells, in particular NK cells, group 2 innate lymphoid cells (ILC2s), monocytes/macrophages, plasmacytoid dendritic cells, and lung

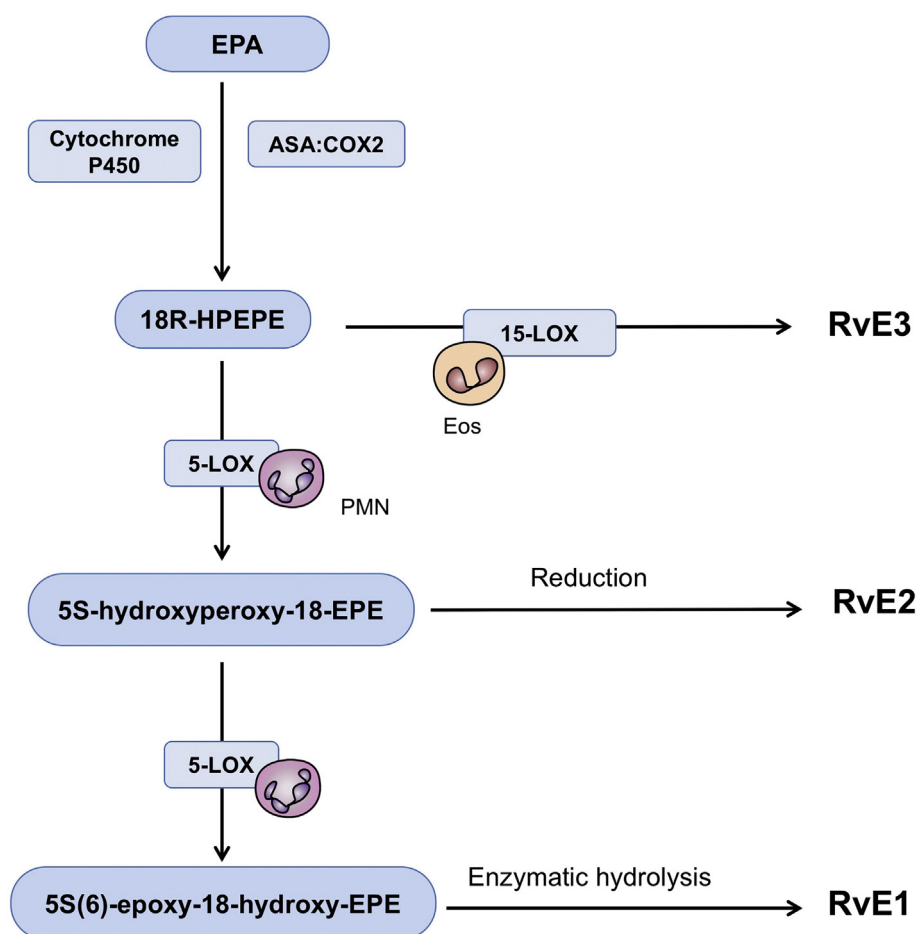


Fig. 6. The biosynthetic pathways for conversion of EPA to E-series resolvins. EPA is converted via aspirin acetylated COX-2 or by cytochrome P450 in microbes to the intermediate 18R-hydroperoxy-eicosapentaenoic acid (18R-HpEPE). The intermediate 18R-HpEPE can be further transformed via neutrophil 5-LOX to an intermediate for subsequent enzymatic conversion to RvE1 or via reduction to RvE2. RvE3 is generated directly from 18R-HpEPE via eosinophil 15-LOX.

epithelial cells (Barnig et al., 2013; Campbell et al., 2007; Cash et al., 2008; Du & Leung, 2009; Parolini et al., 2007; Samson et al., 1998; Wittamer et al., 2003). CMKLR1 was first identified as a receptor for the peptide chemerin. Thus, like ALX/FPR2, CMKLR1 recognizes both lipid and peptide ligands. RvE1 and RvE2 have also been reported as partial agonists and antagonists at the leukotriene B₄ (BLT1) receptor (Arita et al., 2007). The receptor for RvE3 has yet to be identified.

4.3. Anti-asthma therapeutic potential of SPMs

4.3.1. Cell type-specific actions relevant to impaired resolution of inflammation in asthma

Lipoxins, D- and E-series resolvins, protectins, and maresins exhibit cell type-specific actions *in vitro* relevant to resolution of airway inflammation in health (listed in Table 2). These actions include inhibition of eosinophil and neutrophil migration, decrease of T2 cytokine production (e.g. IL-13, IL-5), and enhancement of macrophage phagocytosis of apoptotic eosinophils and neutrophils. In addition to these leukocyte-specific activities, SPMs can directly contribute to tissue repair and healing in the lung through the promotion of basal cell proliferation of the bronchial epithelium, and can limit fibrosis by inhibiting the proliferation of human lung fibroblasts (for references see Table 2).

4.3.2. Potential from animal models

Preclinical evidence for the functional importance of SPMs in resolution of allergic lung inflammation is established in ovalbumin-induced mouse models of allergen sensitization and challenge where stable analogs of SPMs are able to decrease bronchial hyper-reactivity, mucus metaplasia, and type 2 lung inflammation (including eosinophil and T lymphocyte recruitment, Th2 cytokine production, etc.) as well as accelerate the resolution of these parameters after the mice are no longer exposed to allergen (for details and references see Table 3). More recently, the transient receptor potential (TRP) channels expressed on activated lung sensory neurons involved in ILC2 activation have been identified as SPM targets (Park, Lu, et al., 2011; Park, Xu, et al., 2011; Serhan et al., 2012; Talbot et al., 2015).

4.3.3. Studies in human asthma

Several studies in distinct populations of adults and children (reviewed in Table 4) have reported that SPMs are underproduced in the peripheral blood and airways of patients with severe and uncontrolled asthma as well as in asthma exacerbations (Bhavsar et al., 2010; Bonnans et al., 2002; Celik, Erkeköl, Misirligil, & Melli, 2007; Fritscher et al., 2012; Gagliardo et al., 2016; Kazani et al., 2013; Levy et al., 2005; Planaguma et al., 2008; Vachier et al., 2005; Wu, Yin,

Notes to Table 2:

CCR5, CC-chemokine receptor 5; CTGF, connective tissue growth factor; GM-CSF, IFN- γ , interferon- γ ; IL, interleukin; ILC2, group 2 innate lymphoid cells; LPS, lipopolysaccharide; MMP3, matrix metalloproteinase 3; NK, natural killer cell; PKC, protein kinase; PMN, polymorphonuclear leukocyte; TNF, tumor-necrosis factor; Treg, T regulatory; TRPV1, transient receptor potential cation channel subfamily V member 1; VEGF, vascular endothelial growth factor.

Table 2

Cell-type specific actions of SPMs relevant to asthma pathobiology.

Mediator	Target cell	Action(s)	References
LXA ₄	Eosinophil	Inhibits migration and chemotaxis Inhibits generation of eotaxin and IL-5 Counterregulates GM-CSF signaling in eosinophils	Bandeira-Melo et al. (2000); Soyombo, Spur, and Lee (1994); Starosta, Pazdrak, Boldogh, Svider, and Kurosky (2008)
	Neutrophil	Inhibits chemotaxis, trans-endothelial and trans-epithelial migration Inhibits superoxide anion generation and degranulation	Bonnans et al. (2006); Colgan, Serhan, Parkos, Delp-Archer, and Madara (1993); Gewirtz, Fokin, Petasis, Serhan, and Madara (1999); Lee et al. (1989); Levy et al. (1999); Papayianni, Serhan, and Brady (1996); Serhan et al. (1995)
	NK cell	Inhibits NK cell cytotoxicity	Barnig et al. (2013); Ramstedt et al. (1987)
	ILC2	Increases eosinophil and neutrophil induced apoptosis Inhibits IL-13 release	Barnig et al. (2013)
	Monocyte	Stimulates chemotaxis and adhesion Inhibits peroxynitrite generation Reduces IL-8 release	Bonnans et al. (2002); Jozsef, Zouki, Petasis, Serhan, and Filep (2002); Maddox and Serhan (1996)
	Macrophage	Increases engulfment of apoptotic granulocytes	Godson et al. (2000); Mitchell et al. (2002)
	Dendritic cell	Inhibits IL-12 production	Aliberti, Hieny, Reis e Sousa, Serhan, and Sher (2002)
	Bronchial epithelial cell	Stimulates basal cell proliferation after acid injury Inhibits IL-6 and IL-8 release	Bonnans et al. (2006); Bonnans, Mainprice, Chanez, Bousquet, and Urbach (2003)
	Endothelial cell	Stimulates PKC-dependent prostacyclin formation Reduce reactive oxygen species generation Inhibits VEGF-induced migration	Brezinski, Gimbrone, Nicolaou, and Serhan (1989); Cezar-de-Mello, Nascimento-Silva, Villela, and Fierro (2006); Nascimento-Silva, Arruda, Barja-Fidalgo, and Fierro (2007)
	Fibroblast	Inhibits IL-1 β -induced IL-6, IL-8 and MMP3 production Inhibits CTGF-induced proliferation	Sodin-Semrl, Taddeo, Tseng, Varga, and Fiore (2000); Wu, Wu, Lu, Dong, and Chen (2006)
	Smooth muscle	Inhibits LTC ₄ -initiated migration	Parameswaran et al. (2007)
	Eosinophil	Inhibits chemotaxis	Karra, Haworth, Priluck, Levy, and Levi-Schaffer (2015)
	Neutrophil	Inhibits motility Inhibits infiltration	Maddox et al. (1998); Lee et al. (1989)
	Macrophage	Activates macrophage adherence Stimulates motility	Maddox et al. (1998)
LXB ₄	Mast cell	Inhibits degranulation	Karra et al. (2015)
	Neutrophil	Inhibits transepithelial and trans-endothelial migration Inhibition of superoxide generation	Campbell et al. (2007); Hasturk et al. (2006)
	Macrophage	Stimulates non-phagocytic phagocytosis of apoptotic neutrophils Inhibits cytokine production	Schwab, Chiang, Arita, and Serhan (2007); Flesher, Herbert, and Kumar (2014)
	Dendritic cell	Inhibits IL-12 production Inhibits migration Inhibits IL-23 production	Arita, Bianchini, et al. (2005); Arita, Yoshida, et al. (2005) Haworth et al. (2008)
	T cell	Inhibits CCR-5 expression Increases Th17 cells Regulates Th17 cells	Ariel et al. (2006); Haworth et al. (2008)
	Neutrophil	Blocks infiltration	Tjonahen et al. (2006)
	Neutrophil	Inhibits infiltration	Isobe et al. (2012)
	Neutrophil	Inhibits transmigration Stops chemotaxis Blocks adhesion molecules	Sun et al. (2007); Kasuga et al. (2008); Krishnamoorthy et al. (2010)
	Macrophage	Inhibits LPS-induced TNF release Increases phagocytosis of apoptotic cells and allergens Enhances allergen clearance Induce M2 macrophage phenotype	Duffield et al. (2006); Rogerio et al. (2012); Krishnamoorthy et al. (2010)
	B cell	Inhibits IgE production	Kim et al. (2016)
RvD2	Neutrophil	Reduces recruitment by altering receptor expression	Spite et al. (2009)
	Macrophage	Enhances phagocytosis of apoptotic neutrophils	Spite et al. (2009)
	Neutrophil	Blocks transmigration	Dalli, Winkler, et al. (2013)
RvD3	Macrophage	Enhances phagocytosis and efferocytosis	Dalli, Winkler, et al. (2013)
	Neutrophil	Inhibits TNF α and IFN γ release Inhibits PMN transendothelial migration trans-migration	Ariel et al. (2005); Ariel et al. (2006); Bannenberg et al. (2005); Schwab et al. (2007)
PD1	Macrophage	Upregulates CCR-5 expression Stimulates non-phagocytic phagocytosis of apoptotic neutrophils	Schwab et al. (2007)
	T cell	Blocks T cell migration Increases CCR5 expression Promotes T cell apoptosis Inhibits TNF-alpha and IFN-gamma production	Ariel et al. (2005); Ariel et al. (2006)
	ILC2	Inhibits IL-5 and IL-13 production and stimulates amphiregulin production	Krishnamoorthy et al. (2015)
	Neutrophil	Limits infiltration	Serhan et al. (2012)
	Macrophage	Stimulates phagocytosis of apoptotic neutrophils Increase macrophage efferocytosis Enhances the conversion of macrophages from an M1 to M2 phenotype	Serhan et al. (2009); Dalli, Zhu, et al. (2013); Serhan et al. (2012)
Mar1	Treg cell	Induced regulatory T cell formation generation, from naive CD4+ T cells and stimulates amphiregulin production	Krishnamoorthy et al. (2015)
	Bronchial epithelial cell	Inhibits organic dust-induced cytokine production	Nordgren et al. (2013)
	Sensory neuron	Inhibit capsaicin-induced TRPV1 currents	Park, Xu, et al. (2011); Serhan et al. (2012)

Table 3
Biologic activity of SPMs in murine asthma models.

Mediator	Action	Reference
LXA ₄	Inhibits airway hyper-responsiveness and decreases mucus metaplasia Decreases type 2 lung inflammation including eosinophil and T lymphocyte accumulation, IL-4, IL-13, eotaxin, prostanoide and cysteinyl leukotriene production	Levy et al. (2002, 2007)
LXB ₄	Decreases airway hyper-responsiveness and mucus metaplasia Decreases lung eosinophil and T lymphocyte recruitment, IL-4 and IL-13 production	Karra et al. (2015)
RvE1	Decreases lung IL-4 and IL-13 receptor expression Abrogates airway hyperresponsiveness and improves mucus metaplasia Decreases eosinophil and T lymphocyte lung recruitment Prevents Th2 cytokine release (e.g. IL-13) Reduces ovalbumin-specific circulating IgE Regulates NK cell lung migration Enhances IFN- γ production and stimulates LXA ₄ production	Aoki et al. (2008); Haworth et al. (2008, 2011); Flesher et al. (2014); Haworth et al. (2011)
RvD1	Inhibits IL-6 and IL-23 production and reduces survival of IL-17 producing T helper cells Inhibits airway hyper-responsiveness and decreases mucus metaplasia Decreases airway eosinophilia	Rogério et al. (2012)
PD1	Enhances macrophage phagocytosis of allergen from airways Protects from airway hyper-responsiveness and reduces mucus production Decreases airway eosinophil and T cell recruitment	Levy et al. (2007)
Mar1	Decreases IL-13, PGD ₂ and cysteinyl LT production Decreases IL-5 and IL-13 production through Treg suppression of ILC2	Krishnamoorthy et al. (2015)

Zhang, & Tao, 2010). Lipoxin production is lower in patients with aspirin-intolerant asthma (Sanak et al., 2000), and exercise-induced asthma, than in healthy persons (Tahan, Saraymen, & Gumus, 2008). Recently, the mechanism for disruption of lipoxin production was determined to be secondary to increased oxidative stress in uncontrolled asthma (Ono et al., 2014). In addition, a defect in SPM signalling might be involved, as granulocytes in severe asthma display decreased expression of pro-resolving receptors (e.g. ALX/FPR2) (Planaguma et al., 2008).

5. Therapeutic perspectives

Potential therapeutic perspectives that are opened by the new understanding of endogenous resolution pathways are depicted in Fig. 7.

5.1. Glucocorticoids

Many current therapeutic approaches to manage chronic inflammation aim at repressing overactive pro-inflammatory responses by reducing proinflammatory mediator activity, using corticosteroids or biologics. In asthma therapy, inhaled corticosteroids are the main anti-inflammatory treatment for persistent chronic asthma, and many patients experience a reduction of symptoms and decrease in bronchial hyperresponsiveness with corticosteroids (Adams, Bestall, Malouf, Lasserson, & Jones, 2005; Busse et al., 2008; Pauwels et al., 2003). In some circumstances, in addition to their potent anti-inflammatory properties, steroids can display pro-resolving properties. For example,

steroids can increase apoptotic cell engulfment by macrophages (Liu et al., 1999). Glucocorticoids also regulate the expression and function of annexin A1 (lipocortin 1), an anti-inflammatory and pro-resolving molecule that can signal via ALX/FPR2 to counter-regulate the production of pro-inflammatory mediators, and the activities of innate immune cells, in particular neutrophil trafficking (Perretti & D'Acquisto, 2009). In addition, glucocorticoids can also upregulate cellular ALX/FPR2 expression in monocytes and neutrophils (Gilroy et al., 2004; Hashimoto, Murakami, Kitasato, Hayashi, & Endo, 2007).

Of note, inhaled glucocorticoids do not help all patients with asthma and even in those that benefit glucocorticoids do not cure asthma with treatment discontinuation frequently accompanied by a relapse of the disease. There exists a subset of asthma patients (~10–15%) who experience persistent symptoms and/or frequent exacerbations despite high doses of inhaled corticosteroids. These patients have severe asthma with excess morbidity, and are often treated with prolonged systemic corticotherapy with limited therapeutic benefit and many potential side-effects, such as osteoporosis, diabetes, systemic hypertension and impaired immune function (Chung et al., 2014). The immunological responses in these patients are currently being characterized to determine if they would benefit from biological targeted therapies that decrease type 2 inflammation and eosinophilia (Swedin et al., 2017).

5.2. Aspirin

The discovery of the ability of ASA to alter the catalytic properties of COX-2 leading to the synthesis of epimeric versions of LXs or resolvins

Table 4
Defects of SPMs in asthma.

Mediator		Reference
LXA ₄	Severe asthma	Diminished LXA ₄ biosynthesis (blood, induced sputum, BAL, EBC); lower LXA ₄ levels correlates with worse lung function and disease severity
	Asthma exacerbation	Decreased LXA ₄ in EBC during exacerbation
	Exercise induced asthma	Decreased LXA ₄ in plasma of children with exercise induced bronchospasm
	Aspirin-intolerant asthma	Decreased lipoxins in aspirin-intolerant asthmatics compared to aspirin tolerant asthmatics
PD1	Severe asthma	Impaired PD1 production in eosinophils from subjects with severe asthma
	Asthma exacerbation	PD1 is diminished in EBC from subjects with asthma exacerbation

BAL, bronchoalveolar lavage; EBC, exhaled breath condensates.

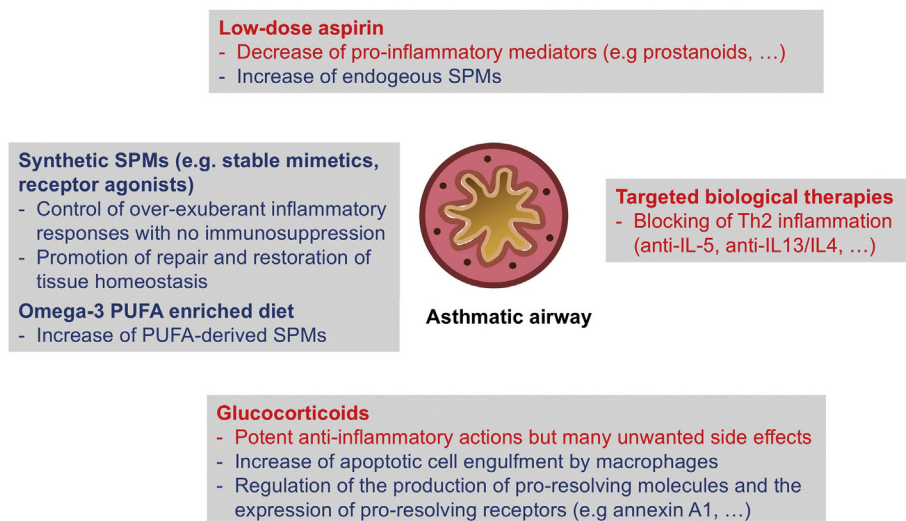


Fig. 7. Potential SPM-based therapeutic perspectives for chronic asthma. Preclinical results from cellular, animal and human studies indicate a potential for SPM-based resolution therapies for prevention and treatment of asthma. Anti-inflammatory (red) and Pro-resolving (blue) actions for SPMs and common medications that intersect with resolution pathways are indicated. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

has revealed this drug as a potential interesting agent to both decrease pro-inflammatory mediators (e.g., prostanoids) and concurrently augment endogenous mediators of resolution (Claria & Serhan, 1995). Investigational proof-of-concept studies have shown that low dose aspirin administration to volunteers increased 15-epi-LXA₄ levels in peripheral blood (Chiang, Bermudez, Ridker, Hurwitz, & Serhan, 2004). Theoretically, the aspirin-triggered increase in lipoxins has the potential to address the deficit in endogenous lipoxin production in patients with severe asthma; however, increased oxidative stress in the severe asthma airway may also impair 15-epi-LXA₄ production (Ono et al., 2014).

5.3. Mimetics to SPMs

Because defective resolution pathways are linked to pathological airway inflammation, complementary therapies that stimulate SPM production have the promise of controlling over-exuberant inflammatory responses, and to promote repair and restore tissue structure and function without unwanted side effects, such as immunosuppression.

5.3.1. Stable synthetic mimetics

Towards this end, stable synthetic mimetics to endogenous SPMs are under development, and in matching studies, these mimetics display similar biological actions to the parent mediators in animal models with an advantage of resisting local inactivation (including mimetics encapsulated in vesicles) (Kasuga et al., 2008; Serhan, Krishnamoorthy, Recchiuti, & Chiang, 2011; Serhan & Petasis, 2011; Sun et al., 2007; Van Dyke et al., 2015). Several of these mimetics are in pre-clinical development programs for different chronic inflammatory conditions (for reviews see Serhan, 2017; Serhan, Chiang, & Dalli, 2015). In a recent double-blind placebo-controlled clinical trial, a topical 15-R/S-methyl-LXA₄ preparation was tested for the treatment of infantile eczema (Wu, Chen, Liu, Wu, & Dong, 2013). In this study, the efficacy of the lipoxin mimetic was at least equivalent to gold standard topical steroid therapy for the reduction of eczema severity by quantitative and qualitative measures. To date, no studies have reported the therapeutic use of any SPM in asthma but it is interesting to observe that LXA₄, when administered to asthmatic subjects *via* nebulization, attenuates LTC₄-induced bronchoconstriction (Christie, Spur, & Lee, 1992).

5.3.2. Synthetic chemical SPM receptor agonists

Synthetic SPM receptor agonists are also under development by several pharmaceutical companies, including ALX/FPR2 agonists (reviewed in Corminboeuf & Leroy, 2015). Recently, a phase 1 study on a first-in-class ALX/FPR2 receptor agonist (ACT-389949) showed this compound to be safe and well tolerated in healthy subjects. Because of the pleomorphic nature of ligand-dependent ALX/FPR2 signaling, the development of receptor agonists for this target is a challenging project. Of note, a biomarker evaluation of ACT-389949 revealed a transient pro-inflammatory rather than anti-inflammatory response, as well as rapid receptor desensitisation, which limits its application as a potential pro-resolving drug (Stalder et al., 2017). Studies from other pharmaceutical companies are ongoing.

5.4. SPM from diet

Dietary delivery of bioavailable omega-3 PUFAs in order to restore levels of specific endogenous pro-resolving mediators is another strategy to potentiate pro-resolving pathways. PUFAs are essential nutrients that are not produced by mammals or humans to any significant extent. Omega-3 fatty acids, mainly EPA and DHA, are found primarily in dietary fish oils and the beneficial cardioprotective and anti-inflammatory effects of fish oil supplementation have been reported (Burr, 1992; Calder, 2013). Dietary interventional studies with omega-3 fatty acids have demonstrated an increase of PUFA-derived pro-resolving lipid mediators in blood and tissues (Barden et al., 2016; Colas, Shinohara, Dalli, Chiang, & Serhan, 2014; Polus et al., 2016; Psychogios et al., 2011). Of interest, chronic lung inflammation in asthma and cystic fibrosis is associated with decreased airway mucosal levels of DHA (Freedman et al., 2004) that would be predicted to adversely impact SPM generation, which has been consistently observed in these conditions (Eickmeier et al., 2017; Karp et al., 2004; Kazani et al., 2013; Levy et al., 2005; Planaguma et al., 2008; Vachier et al., 2005; Yang, Eiserich, Cross, Morrissey, & Hammock, 2012).

Oral omega-3 PUFA supplementation has been shown to decrease systemic and airway inflammation after bronchial allergen challenge (eosinophil markers) and in patients with documented exercise-induced bronchoconstriction (induced sputum differential cell count percentage and concentrations of LTC₄-LTE₄, PGD₂, IL-1β and TNF-α) (Schubert et al., 2009). The endogenous levels of omega-3 PUFAs needed for sufficient SPM production to limit acute inflammation

is currently unknown, as dietary target recommendations were not established with SPM production as a criterion. Further research is needed to assess the relationship between PUFA ingestion and tissue SPM production. These factors as well as the influence of oxidative stress in target tissues, likely account for the variability observed in response to omega-3 PUFA ingestion in clinical trials in asthmatic patients (Calder, 2006; Hodge et al., 1998; Nagakura, Matsuda, Shichijyo, Sugimoto, & Hata, 2000; Woods, Thien, & Abramson, 2002). Thus, there is a need to better understand dose–response relationships between oral intake of PUFA and enrichment of airway mucosal PUFA and their local conversion to SPM.

It is noteworthy that SPMs are present in significant levels in placenta and human milk (Arnardottir, Orr, Dalli, & Serhan, 2016; Keelan et al., 2015; Weiss et al., 2013), which suggests an important role for SPMs in health maintenance during a particularly vulnerable period of infant development. In a recent randomized placebo-controlled study from a Danish birth cohort, supplementation with a high dose of n – 3-LCPUFA (a dose corresponding to a 10–20-times increase of the normal intake) during the third trimester of pregnancy was associated with a significantly lower risk of asthma symptoms and fewer respiratory infections in children at 3 years (Bisgaard et al., 2016). This effect was most prominent among children of women who had low pre-intervention EPA and DHA blood levels (Ramaswami, Serhan, Levy, & Makrides, 2016).

Taken together, these preliminary results indicate a clear potential of SPM-based resolution therapies for prevention and treatment of asthma and other forms of pathological lung inflammation.

6. Conclusion

Asthma is a chronic inflammatory airway disease where recent data indicate insufficient activation of pro-resolving pathways, including defects in SPM production, to contribute to chronicity and severity of the disease. Addressing the observed defect in resolution of airway inflammation represents a potential new therapeutic approach in asthma.

Conflict of interest statement

CB and NF declare no conflicts of interest. B.D.L. is a coinventor on patent 8,119,691 assigned to Brigham and Women's Hospital.

Acknowledgements

This work was funded by US National Institutes of Health grants HL122531, U10HL109172, U01HL108712 and P01GM095467.

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