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DHA- and EPA-derived resolvins, protectins, and maresins in airway inflammation

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Abstract

Essential fatty acids can serve as important regulators of inflammation. A new window into mechanisms for the resolution of inflammation was opened with the identification and structural elucidation of mediators derived from these fatty acids with pro-resolving capacity. Inflammation is necessary to ensure the continued health of the organism after an insult or injury; however, unrestrained inflammation can lead to injury “from within” and chronic changes that may prove both morbid and fatal. The resolution phase of inflammation, once thought to be a passive event, is now known to be a highly regulated, active, and complex program that terminates the inflammatory response once the threat has been contained. Specialized pro-resolving mediators (SPMs) are biosynthesized from omega-3 essential fatty acids to resolvins, protectins, and maresins and from omega-6 fatty acids to lipoxins. Through cell-specific actions mediated through select receptors, these SPMs are potent regulators of neutrophil infiltration, cytokine and chemokine production, and clearance of apoptotic neutrophils by macrophages, promoting a return to tissue homeostasis. This process appears to be defective in several common human lung diseases, such as asthma and COPD, which are characterized by chronic unrestrained inflammation and significant associated morbidity. Here, we highlight translational research in animal models of disease and with human subjects that sheds light on this rapidly evolving area of science and review the molecular and cellular components of the resolution of lung inflammation.

Keywords

Fatty acids; resolution; inflammation; lung

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Conflict Of Interest

B.D.L. is an inventor on patents assigned to Brigham and Women's Hospital; some of these patents (those pertaining to Rvs) are licensed to Resolvix Pharmaceuticals. The interests of B.D.L. were reviewed and are managed by the Brigham and Women's Hospital and Partners HealthCare in accordance with their conflict-of-interest policies. M.G.D. has no conflict of interest to disclose.

1. Introduction

The hallmarks of acute inflammation include specific cellular events, including increased permeability of the endothelium and epithelium, infiltration of polymorphonuclear leukocytes, inflammatory macrophages, and lymphocytes to sites of infection or injury, and subsequent tissue edema (Cotran, 2009). The cellular events of resolution oppose inflammation and in a process known as catabasis return the host tissues to a non-inflammatory state (Serhan et al., 2004). Barrier integrity is restored and the permeability of endothelium and epithelium is reduced; neutrophils cease trafficking to sites of inflammation; macrophages clear the inflammatory milieu by phagocytosis of microbes and apoptotic neutrophils in a process termed efferocytosis (Savill et al., 1989; Schwab et al., 2007); and neutrophils at the mucosal interface are released by CD55 from the apical surface of epithelial cells for luminal clearance (Campbell et al., 2007). As tissue leukocytes recede from sites of acute inflammation, levels of proinflammatory cytokines and chemokines also decrease. At this turning point, metabolism of polyunsaturated fatty acids switches from conversion to pro-inflammatory mediators, such as leukotrienes and prostaglandins, to pro-resolving mediators, such as lipoxins (Levy et al., 2001). These pro-resolving mediators act as agonists at specific receptors to contribute to the restoration of host tissues to a homeostatic state (Serhan, 2014).

Excessive acute inflammation and chronic unresolved inflammation have been linked to important and morbid human lung diseases, including acute respiratory distress syndrome (ARDS), asthma, cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD). Current research is determining whether the ungoverned inflammation in these diseases reflects a failure of the healthy resolution program in the lungs. This review will examine research in animal models of disease in which SPMs have been shown to increase survival and promote resolution of inflammation as well as several human diseases that are associated with dysregulation of SPM pathways, including SPMs generated from docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA).

2. Polyunsaturated fatty acids are available during acute inflammation

Polyunsaturated fatty acids (PUFAs) are known to be essential nutrients that are not produced by humans to any significant extent. The omega 6 PUFA arachidonic acid is incorporated into cellular phospholipids and on cellular activation is liberated by phospholipase A₂ enzymes for enzymatic conversion to prostaglandins, leukotrienes, or lipoxins (Samuelsson et al., 1987; Serhan, 2007). Omega 3 fatty acids are found primarily in dietary fish oils (Burr, 1929; Calder, 2013). The omega 3 PUFAs eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3) are detectable in whole blood from healthy individuals and comprise a small proportion of total fatty acids. EPA levels in blood range from 0.5 to 2.8% of total fatty acids and DHA ranges from 1.3 to 5% (Albert et al., 2002; Gong et al., 1992; Kew et al., 2004; Newcomer et al., 2001; Wakai et al., 2005) varying based on differences in dietary intake. DHA and EPA have long been known to have beneficial health effects including anti-inflammatory, anti-thrombotic, and immunoregulatory properties (De Caterina, 2011; Iigo et al., 1997). DHA and EPA are concentrated in neural tissues including brain and retina as well as in human milk, plasma, and sperm

(Bazan, 2003; Calder, 2013; Crawford et al., 2013). The airway mucosa is also enriched with DHA in health (Freedman et al., 2004). Mechanisms for dietary enrichment of airway mucosal PUFA remain to be determined. These essential omega 3 PUFAs can serve important roles in regulating acute inflammation through their conversion to potent lipid derived pro-resolving mediators (reviewed in (Serhan, 2014)).

DHA and EPA are now known to be available at sites of acute inflammation through several distinct mechanisms. In particular, circulating DHA and EPA in plasma can be detected in inflammatory exudates at the site of tissue injury within minutes of initial injury (Kasuga et al., 2008) (Fig. 1A). DHA and EPA are carried via plasma edema into the inflammatory arena at the tissue level where they are made available for rapid enzymatic conversion into resolvins, protectins, and maresins that are bioactive for tissue inflammation and organ injury (Serhan, 2011). Additionally, on cell activation, DHA and EPA are rapidly released from cell membranes through the activity of select secretory phospholipase A₂ enzymes that hydrolyze phospholipids to release free fatty acids (Murakami et al., 2011) (Fig. 1B).

DHA is highly enriched in brain phospholipids and is an essential component for brain growth; however, DHA cannot be synthesized *in vivo* and must be transported across the blood brain barrier. Recently, a new mechanism for DHA transport across the blood brain barrier was identified in mice where the orphan receptor Mfsd2a is engaged to transport DHA (in the form of lysophosphatidylcholine – LPC) across the blood brain barrier in a Na⁺-dependent fashion (Nguyen et al., 2014) (Fig. 2C).

3. DHA and EPA are enzymatically transformed to SPMs

Essential PUFAs serve an important role in regulating the acute inflammatory response as substrates for enzymatic conversion to potent lipid-derived mediators (Samuelsson et al., 1987). During resolution of a self-limited experimental model of acute inflammation *in vivo*, liquid chromatography tandem mass spectrometry (LC-MS/MS)-based lipid mediator metabolomic profiling revealed that EPA and DHA are enzymatically converted into specific bioactive compounds that display protective anti-inflammatory and pro-resolving activities (reviewed in (Serhan, 2014)). The biosynthetic pathways for conversion of DHA to the D-series resolvins, protectins, and maresins is shown in Fig. 2 and the pathways for conversion of EPA to the E-series resolvins are shown in Fig. 3.

3.1. D-series Resolvins

DHA (C22:6) is enzymatically converted to the D-series resolvins (RvD1-4) through trans-cellular biosynthesis (Fig. 2). During cell-cell interactions in airway inflammation, 15-lipoxygenase (15-LOX) in epithelial cells converts DHA to 17S-hydroperoxy-DHA, which can be subsequently converted by 5-LOX (in neutrophils) to RvD1 through RvD4 via epoxide-containing biosynthetic intermediates (Hong et al., 2003; Serhan et al., 2002) (Fig. 2A). The aspirin triggered resolvins (AT-RvD1-4) are produced after initial conversion of DHA by aspirin-acetylated COX-2 in vascular endothelial cells to 17R-hydroxy-DHA, which can be transformed via neutrophil-derived 5-LOX to the epimeric forms of the resolvins (Serhan et al., 2002). The stereochemistry of some of the D-series resolvins has been established (RvD1 (Sun et al., 2007), RvD2 (Spite et al., 2009), RvD3 (Dalli et al.,

2013a), and additional members (RvD4 through RvD6) have been detected. The D-series resolvins have been detected in blood from healthy individuals and increase with omega 3 fatty acid dietary supplementation (Colas et al., 2014; Oh et al., 2012; Psychogios et al., 2011).

3.2. Protectins

DHA can also be enzymatically converted through 15-LOX action via an epoxide-containing intermediate to the protectin family (also known as neuroprotectins in neural tissues) (Hong et al., 2003; Serhan et al., 2006). Protectin D1 is present in mouse inflammatory exudates, mouse lung, human blood, and human exhaled breath condensates in asthmatic and healthy individuals (Hong et al., 2003; Levy et al., 2007; Serhan et al., 2006).

3.3 Maresins

Macrophage mediators in resolving inflammation, or maresins, are a third major family of DHA-derived SPMs. Maresins are primarily produced in macrophages (Serhan et al., 2009) wherein phagocytosis of apoptotic neutrophils generates SPMs (Freire-de-Lima et al., 2006; Schwab et al., 2007), as well as 14-hydroxy-DHA (14-HDHA) (Serhan et al., 2009). Maresin 1 (MaR1) is generated through conversion of 14-HDHA, via 12-LOX, through a 13,14-epoxide intermediate by human macrophages (Dalli et al., 2013b). MaR1 is also generated during human platelet-neutrophil interaction via platelet 12-LOX conversion of DHA to 13S, 14S-epoxy-maresin followed by neutrophil conversion to MaR1 (Abdulnour et al., 2014).

3.4 Sulfido Conjugates

The DHA metabolome also includes sulfido-conjugates of maresin, protectin, and the D-series resolvins that are bioactive (Dalli et al., 2014; Dalli et al., 2015). These sulfido-conjugate compounds of SPMs are generated by conversion of DHA by activate phagocytes and are active in stimulating the resolution of acute inflammation and promoting tissue regeneration.

3.5 E-series Resolvins

EPA (C20:5) can be enzymatically converted into the E-series resolvins family of SPMs through trans-cellular mechanisms (Fig. 3). EPA is converted to 18R-hydroxyeicosapentaenoic acid (18R-HEPE) by vascular endothelial cells expressing COX-2, which is acetylated in the presence of aspirin during inflammation. 18R-HEPE is then released from endothelial cells and converted via neutrophil-derived 5-LOX through a common epoxy intermediate to RvE1 and RvE2 (Arita et al., 2005a; Ogawa et al., 2009; Oh et al., 2012; Serhan et al., 2000a; Tjonahen et al., 2006). In the absence of aspirin, RvE1 biosynthesis can be initiated through cytochrome p450 enzymatic conversion of EPA (Serhan et al., 2000b). RvE1 has been detected in plasma, sera, and sputum (Arita et al., 2005a; Colas et al., 2014; Yang et al., 2012). RvE3 is distinct from the other E-series resolvins in its biosynthesis, as it is generated via the actions of 12/15-LOX derived from mouse eosinophils (Isobe et al., 2012) rather than neutrophil 5-LOX.

4. Cellular actions of SPMs

Acute inflammation is essential for host defense and survival. Controlling and resolving inflammation to protect vital tissues and organs from collateral damage and further injury is equally as important. The acute inflammatory response resolves in an active way that engages specific cellular events. Neutrophils begin to die via induction of cytokines and T cells undergo activation-induced programmed cell death. SPMs induce the expression of CCR5 on T cells, which scavenges residual proinflammatory chemokines. Macrophages subsequently engulf apoptotic leukocytes clearing the tissue of inflammatory cells and mediators. Efferocytosis also leads to SPM production, which positively feeds back to limit neutrophil migration into the tissues and also enhances further macrophage phagocytosis of apoptotic neutrophils.

In addition to these innate immune effectors, SPMs have actions on multiple lymphocyte subsets. They enhance B cell differentiation into antibody-secreting cells (Ramon et al., 2012), direct NK cell-mediated apoptosis of neutrophils and eosinophils (Barnig et al., 2013) as well as NK cytotoxicity (Haworth et al., 2011), modulate pro-inflammatory cytokine production by innate lymphoid cells (ILCs) (Barnig et al., 2013) and engage regulatory T cells to restrict cytokine production by ILCs (Krishnamoorthy et al., 2014). These findings uncover an interesting and pivotal role for SPMs at the bridge between innate and adaptive immunity during an inflammatory response.

SPMs are active in picogram to nanogram doses and have varied actions that promote control of inflammation, shorten the time interval to resolution, promote healing, and alleviate pain (reviewed in (Serhan, 2014)). The SPMs display stereoselective and cell-type-specific actions, which are discussed below and shown in Table 1.

4.1. D-series Resolvins

RvD1 has been shown to prevent transendothelial migration of neutrophils in a murine model of peritonitis (Sun et al., 2007) and to block integrin adhesion molecules on human neutrophils (Krishnamoorthy et al., 2010). RvD1 also promotes macrophage engulfment and phagocytosis of apoptotic neutrophils (Krishnamoorthy et al., 2010). RvD1 can influence the humoral immune response by increasing production of IgM and IgG from activated B cells (Ramon et al., 2012). RvD1 also enhances macrophage phagocytosis and clearance of allergen in a murine model of allergic airways disease (Rogerio et al., 2012).

RvD2 increases survival in a mouse model of sepsis (Spite et al., 2009). In this model, RvD2 decreases endothelial-leukocyte interactions via nitric oxide production as well as modifying adhesion receptors on leukocytes (Spite et al., 2009). In addition, RvD2 decreases local and systemic bacterial burden, blunts cytokine production and neutrophil recruitment, and increases peritoneal mononuclear cell and macrophage phagocytosis (Spite et al., 2009), all of which contribute to regulation of excessive inflammation.

4.2. Protectins

Protectin D1 is produced from DHA by T helper type 2-skewed PBMCs. Protectin D1 promotes human T cell apoptosis via lipid raft clustering and blocks T cell migration in vivo

(Ariel et al., 2005). Protectin D1 promotes upregulation of CCR5 expression on apoptotic T cells leading to termination of chemokine signaling during the resolution phase of inflammation (Ariel et al., 2006). Protectin D1 also inhibits tumor necrosis factor alpha (TNF-[.Delta]) and interferon-gamma (IFN-[.theta1]) secretion from T cells (Ariel et al., 2005). Protectin D1 is active in human retinal pigment epithelial cells to protect against oxidative stress-induced apoptosis (Mukherjee et al., 2004) and in glial cells to block cytokine production (Hong et al., 2003). Finally, like the D-series and E-series resolvins, protectin D1 has also been described to inhibit transendothelial migration of neutrophils and enhance macrophage efferocytosis of apoptotic neutrophils (Schwab et al., 2007; Serhan et al., 2011).

4.3. Maresins

During the resolution phase of murine peritonitis, maresins are a potent stimulus for macrophage uptake and phagocytosis of apoptotic neutrophils (Serhan et al., 2009). MaR1 acts directly on planaria tissue to promote regeneration and in mice MaR1 reduces neuropathic pain (Serhan et al., 2012). MaR1 reduces lung inflammation and ILC type 2 (ILC2) production of the type 2 cytokines IL-5 and IL-13 (Krishnamoorthy et al., 2014). Regulation of ILC2s is selective as MaR1-mediated inhibition of type 2 cytokines was accompanied by increased production of amphiregulin, which is important in tissue repair (Krishnamoorthy et al., 2014). MaR1 also induces regulatory T cell (Treg)-based suppressive activity for ILC2 and Th2 cells (Krishnamoorthy et al., 2014).

4.4. E-series Resolvins

In a mouse model of peritonitis, apoptotic T cells upregulated CCR5 expression in the presence of RvE1 (Ariel et al., 2006). RvE1 also acts at the mucosal surface to reduce transendothelial migration of neutrophils as well as promote luminal clearance of neutrophils by apical CD55 expression at mucosal sites of acute inflammation (Campbell et al., 2007). RvE1 has activity that promotes a reduction in neutrophils by regulating tissue infiltration, increasing macrophage ingestion of apoptotic neutrophils, and enhancing lymphatic clearance of phagocytes (Schwab et al., 2007). RvE1 dramatically reduces dermal inflammation, peritonitis, dendritic cell migration, and IL-12 production (Arita et al., 2005a) and blocks platelet activation and aggregation (Dona et al., 2008). RvE1 modulates vascular smooth muscle cells towards a more protective phenotype not associated with peripheral arterial disease and atherosclerosis (Ho et al., 2010). RvE1 promotes NK cell mediated clearance of eosinophils and antigen specific T cells (Haworth et al., 2011) and regulates pro-inflammatory cytokine production by dendritic cells and Th17 cells in allergic inflammation (Haworth et al., 2008).

5. SPMs act through specific receptors (Fig. 4)

5.1. ALX/FPR2 Receptor

The ALX/FRP2 receptor is present on human neutrophils, eosinophils, airway epithelium, monocytes, macrophages, T cells, synovial fibroblasts, and intestinal epithelial cells (Bonnans et al., 2006; Chiang et al., 2006; Fiore et al., 1994; Maddox et al., 1997) as well as human NK cells and ILCs (Barnig et al., 2013). Orthologs of the ALX receptor are

expressed in mice (Takano et al., 1997) and rats (Chiang et al., 2003) with preserved structure and function. The ALX receptor is a 7-transmembrane G-protein coupled receptor that interacts with and transmits intracellular signals from LXA₄, 15-epi-LXA₄, RvD1, aspirin-triggered RvD1, and the corticosteroid-induced protein annexin A1 (Chiang et al., 2006; Fiore et al., 1994; Krishnamoorthy et al., 2012; Krishnamoorthy et al., 2010). ALX receptor expression on cells is regulated by inflammatory mediators, transcription factors, and epigenetic mechanisms. LXA₄ itself increases ALX expression by activating its promoter in a positive-feedback fashion (Simiele et al., 2012). Intriguingly, single-nucleotide polymorphisms in the ALX receptor promoter decrease its activity and are associated with increased cardiovascular risk (Simiele et al., 2012). Additionally, in severe asthma there is a deficit in generation of LXA₄ and granulocytes have decreased expression of surface ALX (Levy et al., 2012), suggesting an association with defective signaling through ALX and chronic lung inflammation.

5.2. ERV (CMKLR1) Receptor

The chemokine receptor-like 1 (CMKLR1; also known as ChemR23 and now E-series resolvin (ERV) receptor) is expressed in brain, kidney, cardiovascular, GI, and myeloid tissues (Arita et al., 2005a) and in particular on NK cells, ILCs, macrophages, dendritic cells, and epithelial cells (Barnig et al., 2013; Campbell et al., 2007; Cash et al., 2008; Du and Leung, 2009; Parolini et al., 2007). The ERV receptor is also a 7-transmembrane G-protein coupled receptor that interacts with and transmits intracellular signals from the peptide mediator chemerin as well as RvE1. RvE2 binds to human neutrophils with strong affinity and likely shares receptors with RvE1 (Oh et al., 2012).

ERV is expressed in the lung by both leukocytes and structural cells and signaling through ERV plays pivotal roles in the regulation of innate and adaptive immune cell activation in the lung. In particular, ERV may play a significant role in anti-viral immunity. ERV knock out mice have increased mortality, delayed viral clearance, and increased neutrophilic infiltration and worse lung function compared to controls in a murine model of viral pneumonia (Bondue et al., 2011).

5.3. BLT1 Receptor

The leukotriene B₄ receptor 1 (BLT1) is expressed on human neutrophils, eosinophils, monocytes, macrophages, mast cells, dendritic cells, and T cells (Yokomizo et al., 1997). RvE1 and RvE2 are antagonists at the BLT1 receptor, and have counterregulatory effects that lead to inhibition of neutrophil chemotaxis, calcium mobilization, and NF-κB activation (Arita et al., 2005a; Arita et al., 2007).

5.4. DRV1 Receptor

The G-protein coupled receptor 32 (GPR32; now known as the RvD1 receptor—DRV1) is expressed on human neutrophils, lymphocytes, macrophages, and monocytes as well as vascular tissues (Krishnamoorthy et al., 2010). RvD1, its aspirin triggered epimer AT-RvD1, RvD3, and RvD5 have all been shown to bind and signal through the DRV1 receptor (Chiang et al., 2012; Dalli et al., 2013a; Krishnamoorthy et al., 2012; Krishnamoorthy et al., 2010; Sun et al., 2007). It appears that RvD1 differentially interacts with the DRV1 receptor

during periods of homeostasis and the ALX receptor during the resolution phase of inflammation (Krishnamoorthy et al., 2012).

5.5. DRV2 Receptor

The G-protein coupled receptor 18 (GPR18; known now as the RvD2 receptor—DRV2) is expressed on human and murine neutrophils, monocytes, and macrophages (Chiang et al., 2015). RvD2 binds to and signals through the DRV2 receptor to limit neutrophil infiltration, enhance phagocyte clearance of bacteria, and promote tissue resolution in a murine model of acute inflammation (Chiang et al., 2015).

5.6. Other Receptors

The molecular identification of the receptors through which protectin D1 signals has not yet been elucidated. Protectin D1 activity is cell-type specific, with a structure activity relationship suggestive of the presence of one or more receptors. Protectin D1 binds to neutrophils at high- and low-affinity binding sites as well as retinal epithelial cells (Marcheselli et al., 2010). The molecular identification of the receptors through which MaR1 signals has also not yet been elucidated; however, MaR1 can block the transient receptor potential V1 (TRPV1) signaling in primary sensory neurons thus reducing inflammatory and neuropathic pain in vivo in mice (Serhan et al., 2012). Studies are ongoing to further define the receptors through which the maresins exert their effects.

6. Human lung diseases are associated with decreased SPMs

In humans, the actions of the resolvins, protectins, and maresins in vivo are just beginning to be investigated. RvD1, RvD2, and RvE1 can be detected in samples of peripheral venous blood from healthy individuals and their levels are modified by omega-3 fatty acid dietary supplementation (Colas et al., 2014; Mas et al., 2012; Psychogios et al., 2011). A recent study has described the upregulation of RvD1 and RvD2 in the plasma of patients recently diagnosed with pulmonary tuberculosis (Frediani et al., 2014). Importantly, RvE1 has also been detected in human milk (Weiss et al., 2013). This conveyance of SPMs from mother to child is strong suggestive evidence of their protective activities. SPMs are also detectable in serum and CSF from patients with multiple sclerosis (Pruss et al., 2013), plasma of patients with IgA nephropathy (Zivkovic et al., 2012), and in sputum from adults with cystic fibrosis (Yang et al., 2012). Protectin D1 is present in serum and cerebrospinal fluid of patients with multiple sclerosis (Pruss et al., 2013), exhaled breath condensates from asthmatics (Levy et al., 2007) and embryonic stem cells (Yanes et al., 2010). Finally, MaR1 has been detected in synovial fluid of patients with rheumatoid arthritis (Giera et al., 2012).

Common lung diseases such as asthma and COPD are characterized in part by unrestrained and chronic inflammation that fails to resolve. Several studies, which we review in this section and Table 2, have identified deficiencies in levels of SPMs in the setting of common human inflammatory lung diseases, suggesting that an insufficiency in the activity of these SPMs in the resolution phase of acute inflammation may perpetuate the chronic inflammation and underlie the pathobiology of these diseases.

Severe asthmatic patients have decreased levels of arachidonic acid (i.e., omega-6 PUFA) derived LXA₄ in blood, induced sputum, bronchoalveolar lavage fluid, and exhaled breath condensates that in some cases has correlated with severity of disease (i.e., FEV1) (Bhavsar et al., 2010; Kazani et al., 2013) (Celik et al., 2007; Fritscher et al., 2012; Levy et al., 2005; Planaguma et al., 2008; Vachier et al., 2005). LXA₄ is reduced in the exhaled breath condensates of children with status asthmaticus in the pediatric intensive care unit compared to controls (Hasan et al., 2012). Children with exercise-induced asthma have lower levels of LXA₄ in plasma after exercise challenge compared to those asthmatics not triggered by exertion (Tahan et al., 2008). Asthmatic individuals who are aspirin-intolerant have a more frequent and severe respiratory symptoms and a lower biosynthetic capacity to generate lipoxins compared to aspirin-tolerant asthmatic patients or controls, which may contribute to their more severe clinical phenotype (Celik et al., 2007; Sanak et al., 2000; Yamaguchi et al., 2011). In addition to asthmatic individuals, moderate to severe COPD patients also have reduced levels of LXA₄ in exhaled breath condensates (Fritscher et al., 2012). During exacerbations in glucocorticoid-resistant COPD patients, serum amyloid A levels are markedly increased and because serum amyloid A can pirate ALX/FPR2 receptors to promote inflammation, it opposes the counter-regulatory mechanisms of LXA₄ at the ALX receptor, which leads to steroid-refractory inflammation in pre-clinical murine models of airway inflammation (Bozinovski et al., 2012).

LXA₄ is present in exudative pleural effusions from human subjects with pleural disease and is associated with pleural exudates that are rich in neutrophils (Levy et al., 2001). Endogenous levels of LXA₄ in BAL fluid from human lung transplant recipients correlates with the severity of both airway and vascular rejection, suggesting a role for SPMs in regulating immune-mediated mechanisms of organ rejection (Levy et al., 2011).

In health, the airway mucosa is enriched with DHA. Of interest, mucosal levels of DHA decrease in asthma and cystic fibrosis (Freedman et al., 2004), which would adversely impact the generation of DHA-derived SPMs such as D-series resolvins, maresins, and protectins. Levels of EPA-derived RvE1 in respiratory secretions from adults with CF correlated with better lung function (i.e., FEV1) compared to those patients with undetectable levels of RvE1 (Yang et al., 2012). Lipoxin levels in airway secretions (Karp et al., 2004; Yang et al., 2012) and platelets (Mattoscio et al., 2010) from patients with CF are significantly suppressed compared with controls, and can be increased by antibiotic therapy (Chiron et al., 2008). In a mouse model of CF, exogenous administration of a lipoxin analog suppresses neutrophilic inflammation, decreases pulmonary bacterial burden and attenuates disease severity (Karp et al., 2004).

Protectin D1 is an anti-inflammatory and pro-resolving molecule synthesized by human eosinophils; however, levels of protectin D1 are significantly lower in exhaled breath condensates from subjects with asthma exacerbations (Levy et al., 2007), and eosinophils from patients with severe asthma have decreased protectin D1 production, even in presence of exogenous DHA (Miyata et al., 2013).

Patients with scleroderma lung disease have an upregulation of pro-inflammatory molecules such as leukotrienes in the lungs that are not balanced by a concomitant upregulation of anti-inflammatory or pro-resolving molecules such as LXA₄ (Kowal-Bielecka et al., 2005).

Additional studies assessing the presence and activity of SPMs in other human pulmonary diseases such as viral infection, acute respiratory distress syndrome, interstitial lung disease, idiopathic fibrosis, lung cancer and tuberculosis as well as diseases of the pulmonary vasculature such as pulmonary hypertension are warranted.

7. SPMs in animal models of disease

7.1. Allergic asthma

In mouse models of allergic asthma/airway inflammation, SPMs display potent immunomodulatory actions (Table 3). In acute and chronic allergen-driven models, RvE1 promotes the resolution of inflammatory airway responses by inhibiting airway eosinophil and lymphocyte recruitment, suppressing the production of IL-6, IL-13, and IL-23, promoting LXA₄ and IFN- γ production, and decreasing airway hyperresponsiveness to inhaled methacholine (Fletcher et al., 2014; Haworth et al., 2008). When administered prior to allergen challenge, RvE1 also has anti-inflammatory effects, including decreasing airway eosinophilia and lymphocyte recruitment and decreasing type 2 cytokine secretion (Aoki et al., 2008). RvD1 markedly decreases airway eosinophilia and mucus metaplasia, shortens the resolution interval for lung eosinophilia, significantly enhances macrophage phagocytosis of allergen from the airways, and potently regulates NF- κ B activity (Rogerio et al., 2012).

When protectin D1 is administered before aeroallergen challenge in a murine asthma model, airway eosinophil and T cell recruitment is decreased, airway mucous and levels of pro-inflammatory mediators (including IL-13, cysteinyl leukotrienes and PGD₂) are decreased, and airway hyperresponsiveness to inhaled methacholine is dampened (Levy et al., 2007). When protectin D1 is given later, after aeroallergen challenge, the resolution phase of inflammation is markedly accelerated (Levy et al., 2007). MaR1 decreases ILC2 cytokine production and augments the generation of regulatory T cells for anti-inflammatory and pro-resolving actions, respectively (Krishnamoorthy et al., 2014).

7.2. Pneumonia/Acute Lung Injury

In mouse models of pneumonia and acute lung injury, SPMs also display protective actions (Table 3). In a model of aspiration pneumonia where mice receive intratracheal hydrochloric acid followed by *Escherichia coli*, RvE1 was important in resolving sterile and infectious lung inflammation (Seki et al., 2010). Animals who received RvE1 had significantly decreased lung levels of pro-inflammatory cytokines, including IL-1[.Epsilon], enhanced bacterial clearance, decreased lung neutrophil trafficking, and improved survival (Seki et al., 2010).

In a mouse model of LPS-induced acute lung injury, pretreatment of animals with RvD1 prior to LPS exposure is protective (Wang et al., 2011). RvD1 exposure decreases mortality, improves lung pathological changes, inhibits LPS-induced increases in neutrophil and

mononuclear leukocytes recruitment, and inhibits TNF- α and IL-6 production in the BAL fluid (Wang et al., 2011). The RvD1 epimer AT-RvD1 is protective in an acid-injury model of acute lung injury. AT-RvD1 reduces BAL fluid neutrophils by ~75% and inhibits neutrophil-platelet interactions by downregulating both P-selectin and its ligand CD24 (Eickmeier et al., 2013). Animals treated with AT-RvD1 had improved epithelial and endothelial barrier integrity and decreased airway resistance associated with increased BAL fluid levels of epinephrine (Eickmeier et al., 2013). AT-RvD1 also significantly decreased levels of BAL fluid pro-inflammatory cytokines, including IL-1 β , IL-6, and TNF- α (Eickmeier et al., 2013). Second organ lung injury following reperfusion after ischemia is mediated in part by activated neutrophils that have difficulty navigating the pulmonary capillary bed, leading to local release of several potentially injurious molecules (e.g., proteases, reactive oxygen species and lipases). In murine hind-limb ischemia/reperfusion models, RvD1 analogues and RvD2 provide significant protection against secondary lung damage by controlling leukocyte activation and infiltration by approximately 50% (Chiang et al., 2015; Kasuga et al., 2008).

A mouse model of lethal influenza infection has shown that protectin D1 is a strong inhibitor of viral replication and leads to improved survival in those animals with severe disease (Morita et al., 2013). In a murine model of ARDS, early MaR1 production occurs in the vascular bed and is dependent on platelet-neutrophil interactions (Abdulnour et al., 2014). MaR1 production is associated with lung protective effects, including decreased neutrophil trafficking to lung, decreased production of inflammatory mediators, and reduced lung edema and tissue hypoxia (Abdulnour et al., 2014).

7.3. Other models of disease

In mouse models of peritonitis, RvE1 (Arita et al., 2005a; Bannenberg et al., 2005), RvD1 (Norling et al., 2012; Recchiuti et al., 2011), and MaR1 (Serhan et al., 2009) have all been demonstrated to limit recruitment of neutrophils to site of inflammation, promote lymphatic removal of phagocytes, inhibit pro-inflammatory cytokine production and generally accelerate the resolution of inflammation. In a murine model of colitis, maresin 1 decreases inflammatory cytokines and promotes the M2 phenotype of macrophages (Marcon et al., 2013).

RvD1 (Murakami 2011) and RvD2 (Spite 2009) both reduce the release of pro-inflammatory cytokines and reducing neutrophil trafficking to sites of inflammation in models of septic shock and RvD2 protects against death (Spite 2009). In murine models of significant trauma from burns, RvD2 administered after a burn prevents secondary thrombosis and necrosis of tissue (Bohr et al., 2013) and improves survival (Kurihara et al., 2013).

RvE1 improves survival in models of colitis (Arita et al., 2005b; Ishida et al., 2010), protects against neovascularization in a model of retinopathy (Connor et al., 2007), protects against reperfusion injury in a model of heart ischemia (Keyes et al., 2010), and leads to prolonged survival of allograft in a model of solid organ transplant (Levy et al., 2011).

In a mouse model of cigarette exposure RvD1 promotes differentiation of alternatively activated (M2) macrophages and neutrophil efferocytosis and accelerates the resolution of

lung inflammation (Hsiao et al., 2013). RvD1 also improves macrophage phagocytosis of amyloid beta protein in a murine model of Alzheimer's disease (Mizwicki et al., 2013).

8. Conclusions

In order to maintain health, the body must respond to a wide array of insults including injury, infection, and noxious stimuli. In particular, the lung is exposed to this milieu of agents potentially through each breath. The host needs to respond to respiratory pathogens and allergens as well as toxins and irritants by mounting an acute inflammatory response to resolve the insult in a timely manner and restore homeostasis. If there is a failure of catabasis to resolve the acute immune response, then overly exuberant acute inflammation or conversion to chronic inflammation may ensue. The pathobiology of several common lung diseases, such as asthma, COPD, and cystic fibrosis, is linked to a chronic inflammatory state that fails to resolve. Similarly, unrestrained acute lung inflammation, as in acute respiratory distress syndrome, may also result from impaired resolution pathways.

The omega-3 fatty acids DHA and EPA and the omega-6 fatty acid arachidonic acid are available at sites of acute inflammation where they are converted into bioactive SPMs. These SPMs are comprised of several distinct families, including the omega-6 PUFA derived lipoxins, and the omega-3 PUFA derived D-series resolvins, E-series resolvins, protectins, and maresins. The SPMs act at subnanogram doses on specific receptors on diverse cells of the immune system, including neutrophils, macrophages, endothelial and epithelial cells, and lymphocytes. The actions of SPMs direct key features of inflammation resolution including inhibition of neutrophil migration, enhancement of macrophage phagocytosis of apoptotic neutrophils, and suppression of pro-inflammatory cytokines and chemokines. There are several reports in preclinical animal models of disease that demonstrate important roles for SPMs in modulating pathobiology and promoting a return to homeostasis after infection or injury leading to improved outcomes, including survival. Common and important human diseases are associated with decreased levels of SPMs including uncontrolled asthma, COPD, and cystic fibrosis. Of great interest, a recent clinical trial of SPMs in humans showed that topical 15-epi-LXA₄ significantly reduced skin inflammation and symptoms in patients with infantile eczema with efficacy that was at least equivalent to the current clinical gold standard therapy topical steroids (Wu et al., 2013), supporting the therapeutic potential of SPMs. Further study of human diseases in the context of inflammation resolution is likely to inform potential new avenues for therapeutic intervention in several common, morbid, and sometimes fatal diseases.

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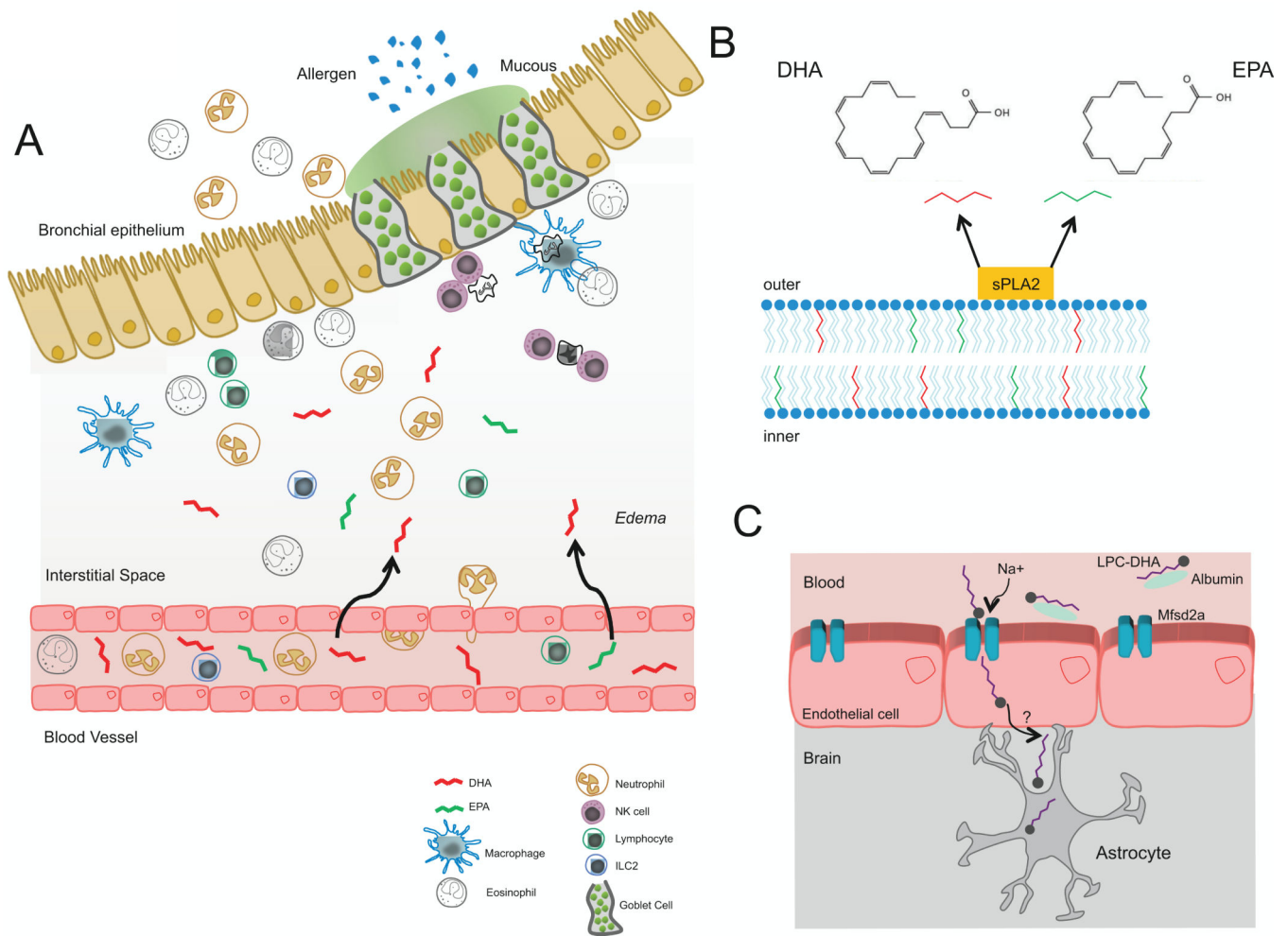


Fig. 1. EPA and DHA are available at sites of acute inflammation. A) The omega-3 fatty acids EPA and DHA circulate in plasma. On injury they move with edema into the tissue sites of acute inflammation where they are converted to exudate SPMs to interact with local immune cells. Shown is a cartoon representation of acute lung inflammation in the setting of allergic asthma. B) DHA and EPA can also be released from the cell membranes through the actions of secretory phospholipase A₂ (sPLA₂). C) DHA (as LPC) is transported across the blood brain barrier via the transporter Mfsd2a.

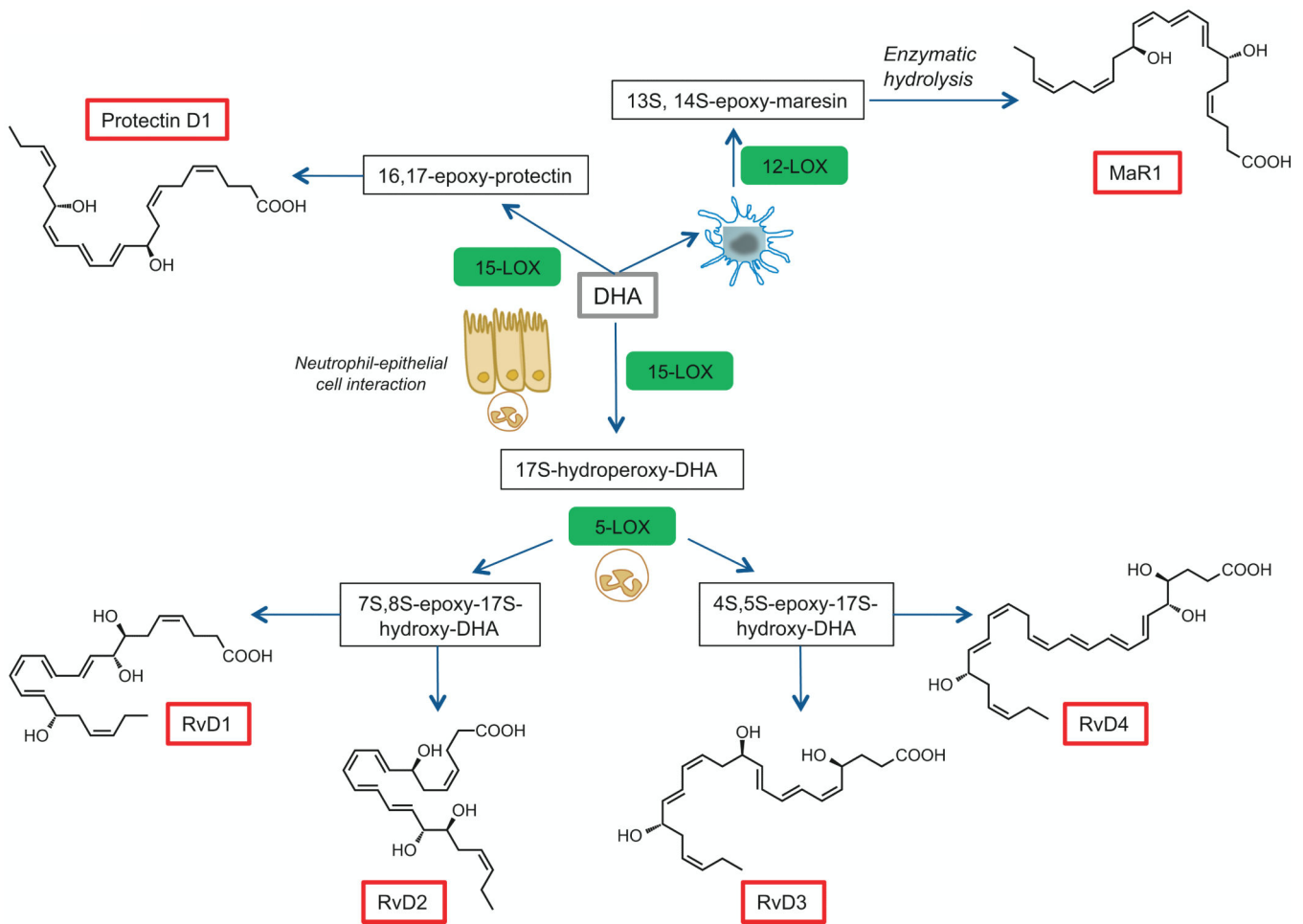


Fig. 2. Biosynthesis of D-series resolvins, maresins, and protectins. Docosahexaenoic acid (DHA; C22:6n-3; grey box) is converted by 15-LOX to the intermediate 17S-hydroperoxy-DHA which is then further converted by neutrophil derived 5-LOX to the D-series resolvins, RvD1 through RvD4. DHA can also be converted via 15-LOX into a 16, 17-epoxy-protectin intermediate and then onto to protectin D1. DHA is converted via 12-LOX in macrophages to a 13S, 14S-epoxy-maresin and then through enzymatic hydrolysis to MaR1.

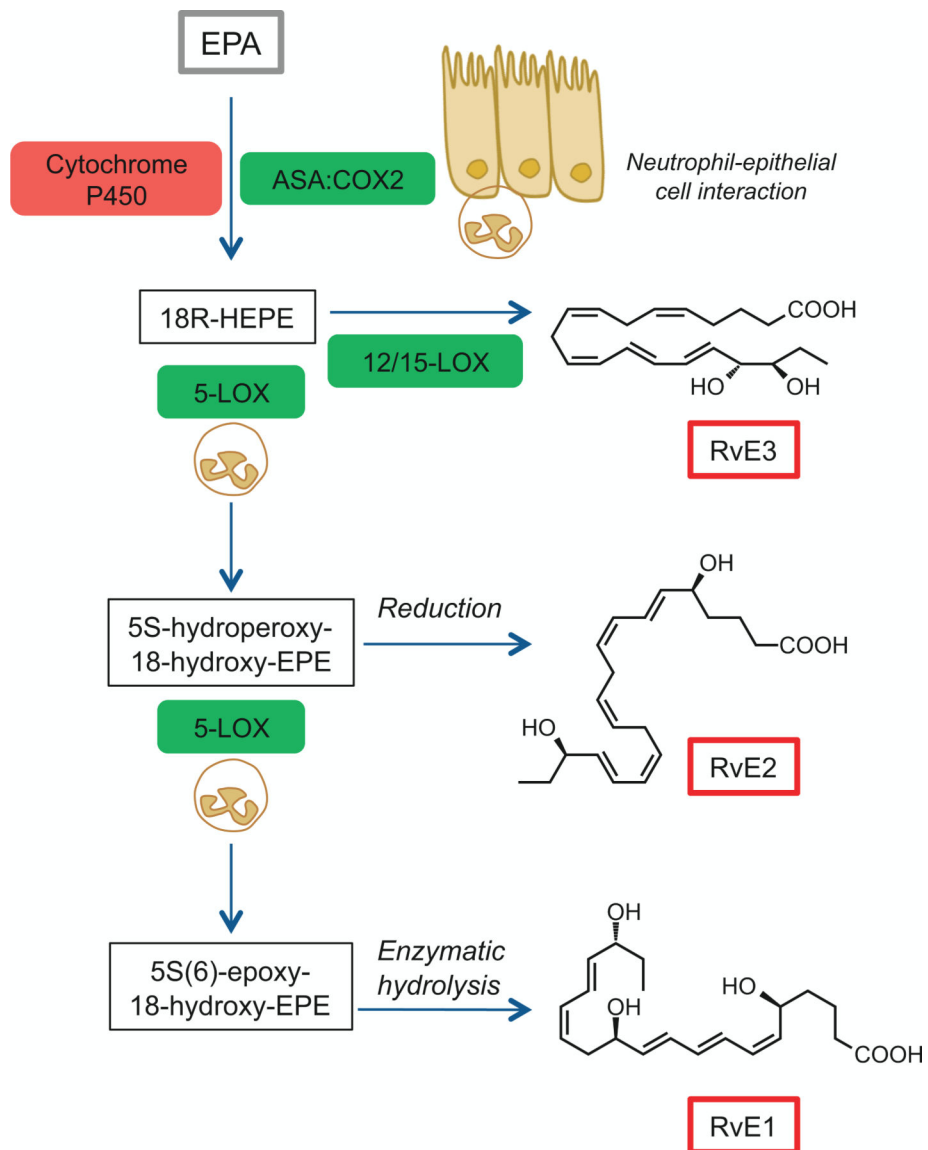


Fig. 3. Biosynthesis of E-series resolvins. Eicosapentaenoic acid (EPA; C₂₀:5n-3; grey box) is converted via aspirin acetylated COX-2 or by cytochrome p450 in microbes to the intermediate 18R-hydroperoxy-EPE (18R-HEPE). The intermediate 18R-HEPE can be further transformed via neutrophil 5-LOX to an intermediate for subsequent enzymatic conversion to RvE1 or via reduction to RvE2. RvE3 is generated directly from 18R-HEPE via 12/15-LOX.

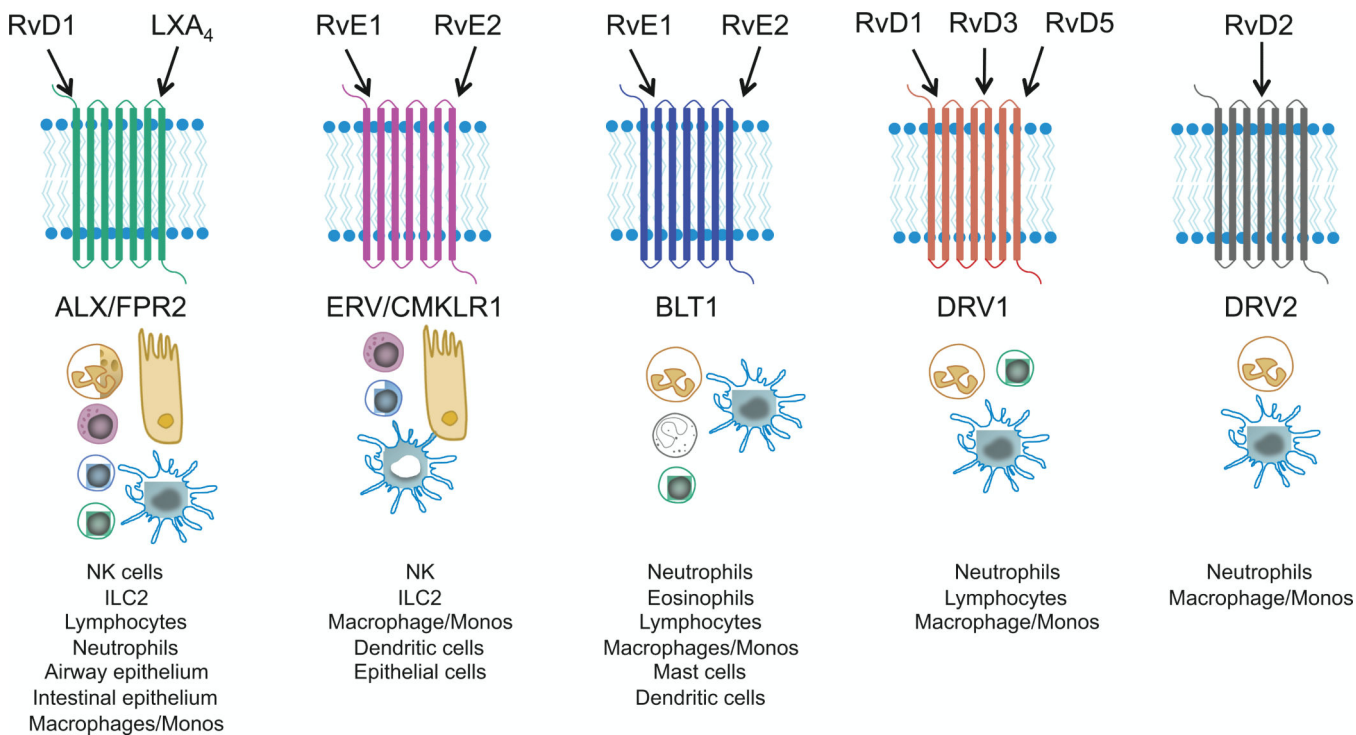


Fig. 4. Cellular targets and receptors for resolvins, protectins, and maresins. SPMs signal through specific 7-transmembrane G-protein coupled receptors. Lipoxin A4 (LXA₄) and the D-series resolvins, in particular RvD1 are agonists for the ALX/FPR2 receptor that is present on a wide variety of leukocytes and other cells. RvE1 and RvE2 are agonists for the CMKLR1/ERV receptor, which is widely expressed on immune cells, and antagonists at the BLT1 receptor. The D-series resolvins are also agonists at the DRV1 and DRV2 receptors. The receptors for protectins and maresins have yet to be molecularly characterized. SPMs signal through these specific receptors to exert influence on leukocytes including halting neutrophil trafficking, promoting macrophage phagocytosis of apoptotic cells and microbes, and blocking further pro-inflammatory cytokine and chemokine production.

Table 1

Cell-based actions of resolvins, protectins and maresins.

SPM	Cell Type	Action	Reference
Resolvin E1	T cells	Increases CCR5 expression; Regulates Th17 cells	Ariel et al 2006; Haworth et al 2008
	Neutrophils	Inhibits trans-migration and promotes clearance	Campbell et al 2007
	Macrophages	Enhances phagocytosis of apoptotic neutrophils	Schwab et al 2007
	NK Cells	Promotes clearance of eosinophils and neutrophils	Haworth et al 2011
	Dendritic Cells	Inhibits IL-23 release; Reduces migration and IL-12 production	Haworth et al 2008; Arita et al 2005
	Platelets	Reduces activation and aggregation	Dona et al 2008
	Vascular smooth muscle	Confers a protective phenotype switch by decreasing PDGF-stimulated migration	Ho et al 2010
Resolvin D1	Neutrophils	Inhibits trans-migration; Stimulates rapid shape change and halts chemotaxis; Blocks adhesion molecules	Sun et al 2007; Kasuga 2008; Krishnamoorthy et al 2010
	Macrophages	Enhances phagocytosis of apoptotic neutrophils; Enhances allergen clearance	Krishnamoorthy et al 2010; Rogerio et al 2012
	B cells	Promotes IgM and IgG production	Ramon et al 2012
Resolvin D2	Neutrophils	Reduces recruitment by altering adhesion receptor expression	Spite et al 2009
	Macrophages	Enhances phagocytosis of apoptotic neutrophils	Spite et al 2009
	Endothelial cells	Reduces leukocyte: endothelial interactions through NO production	Spite et al 2009
Protectin D1	T cells	Blocks T cell migration; Increases CCR5 expression; Promotes T cell apoptosis; Inhibits TNF- α and IFN- γ production	Ariel et al 2005; Ariel et al 2006
	Neutrophils	Inhibits trans-endothelial migration	Schwab et al 2007; Serhan et al 2011
	Macrophages	Promotes efferocytosis of apoptotic neutrophils	Schwab et al 2007; Serhan et al 2011
	Epithelial cells	Protects against oxidative-stress induced apoptosis (retinal pigment epithelium)	Mukherjee et al 2004
	Glial cells	Reduces cytokine production	Hong et al 2003
Maresin 1	Macrophages	Stimulates phagocytosis of apoptotic neutrophils	Serhan et al 2009
	Platelet-neutrophil aggregates	Decreases lung neutrophils, edema, tissue hypoxia, and proinflammatory mediators	Abdulnour et al 2014
	Innate lymphoid cells (type 2)	Reduces expression of IL-5 and IL-13; increases amphiregulin	Krishnamoorthy et al 2014
	Regulatory T cells (Tregs)	Augments Treg generation leading to ILC2 effects	Krishnamoorthy et al 2014

Table 2

Human lung diseases associated with decreased levels of SPMs

SPM	Disease	Finding	Reference
Resolvin E1	Cystic Fibrosis	Decreased RvE1 in CF patients with lower lung function	Yang et al 2012
Protectin D1	Asthma Exacerbation	Decreased PD1 in uncontrolled asthma Decreased PD1 in eosinophils in severe asthma	Levy et al 2007 Miyata et al 2013
Lipoxin A4	Severe Asthma	Decreased LXA ₄ biosynthesis in severe asthma (blood, sputum, BAL); Lower LXA ₄ levels in exhaled breath condensates correlates with worse lung function	Levy et al 2005; Vachier et al 2005; Celik et al 2007; Planaguma et al 2008; Bhavsar et al 2010; We et al 2010; Fritscher et al 2012; Kazani et al 2013.
	Asthma Exacerbation	Decreased LXA ₄ in exhaled breath condensates during exacerbation	Hasan et al 2012
	Exercise-induced Asthma	Decreased LXA ₄ in plasma of children with exercise induced bronchospasm	Tahan et al 2008
	Aspirin-intolerant asthma	Decreased lipoxins in aspirin-intolerant asthmatics compared to aspirin tolerant asthmatics	Sanak et al 2000; Celik et al 2007; Yamaguchi et al 2011
	COPD	Reduced LXA ₄ detected in exhaled breath condensates; serum amyloid A opposes LXA ₄ at ALX	Fritscher et al 2012; Bozinovski et al 2012
	Cystic Fibrosis	Decreased LXA ₄ production and defective lipoxin activity	Karp et al 2004; Chiron et al 2008; Mattoscio et al 2010; Yang et al 2012
	Pleural Effusions	LXA ₄ present in exudative effusions and correlates with neutrophils	Levy et al 2001
	Lung Transplant	LXA ₄ present in BAL fluid during rejection	Levy et al 2011
	Scleroderma	Decreased LXA ₄ levels in BAL of patients with scleroderma lung disease	Kowal-Bielecka et al 2005

Table 3

Actions in vivo for SPMs in animal models of disease

SPM	Disease Model	In vivo action	Reference
Resolvin E1	Pneumonia	Enhances bacterial clearance; Decreases lung neutrophils; Improves survival	Seki et al 2010
	Allergic Airway Inflammation	Enhances T cells and eosinophil clearance; Abrogates airway hyperresponsiveness; Improves mucous metaplasia; Prevents Th2 cytokine release; Enhances IFN- γ production; Suppresses macrophage cytokine production	Haworth et al 2008; Aoki et al 2008; Flesher et al 2014
	Acid-induced acute lung injury	Decreases neutrophil trafficking to lung; Attenuates pro-inflammatory mediators	Seki et al 2010
	Colitis	Decreases neutrophil recruitment; Down-regulates pro-inflammatory gene expression; Improves survival	Arita et al 2005b; Ishida et al 2010
	Peritonitis	Inhibits neutrophil recruitment; Promotes lymphatic removal of phagocytes; Regulates chemokine/cytokine production	Arita et al 2005a; Bannenberg et al 2005
	Retinopathy	Protects against pathological neovascularization	Connor et al 2007
	Heart ischemia	Protects against reperfusion injury after hypoxia	Keyes et al 2010
	Solid organ transplant	Preserves organ function; prolongs survival of allograft	Levy et al 2011
Resolvin D1	Acute lung injury (acid-induced) *	Decreases PMNs; Reduces pro-inflammatory cytokines; Improves barrier integrity; Reduces airway resistance	Eickmeier et al 2013
	Acute lung injury (LPS-induced)	Decreases PMN recruitment; reduces TNF- α and IL-6 production; Reduces mortality	Wang et al 2011
	Allergic airway inflammation	Decreases airway eosinophilia and mucus metaplasia; Enhances macrophage phagocytosis of allergen from airways	Rogério et al 2012
	Secondary lung injury	Reduces second organ injury in ischemia/reperfusion models by inhibiting neutrophil migration	Kasuga et al 2008
	Cigarette induced lung inflammation	Promotes M2 macrophages and neutrophil efferocytosis; Accelerates resolution of inflammation	Hsiao et al 2013
	Septic Shock	Suppresses release of inflammatory cytokines	Murakami et al 2011
	Alzheimer's disease	Stimulates phagocytosis of amyloid- β by macrophages	Mizwicki et al 2013
Resolvin D2	Sepsis	Reduces inflammatory cytokine release; Enhances bacterial clearance; Improves survival	Spite et al 2009
	Secondary lung injury	Reduces second organ injury in ischemia/reperfusion models by inhibiting neutrophil migration	Chiang et al 2015
	Burn wound	Prevents secondary thrombosis and necrosis	Bohr et al 2013; Kurihara et al 2013
Protectin D1	Influenza (H1N1) infection	Inhibits viral replication and reduces severity of disease	Morita et al 2013
	Allergic airway inflammation	Enhances eosinophil and T cell clearance from lung	Levy et al 2007
Maresin 1	ARDS	Decreases lung neutrophils, edema, tissue hypoxia, and inflammatory mediators; Dependent on platelet/neutrophil interactions	Abdulnour et al 2014
	Allergic airway inflammation	Restrains airway inflammation through Treg suppression of ILC2 cytokine production	Krishnamoorthy et al 2014
	Peritonitis	Reduces neutrophil recruitment	Serhan et al 2009

SPM	Disease Model	In vivo action	Reference
	Colitis	Promotes macrophage M2 phenotype; Decreases inflammatory cytokines	Marcon et al 2013

* AT-RvD1

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