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Quenching the fires: Pro-resolving mediators, air pollution, and smoking

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ABSTRACT

Exposure to air pollution and other environmental inhalation hazards, such as occupational exposures to dusts and fumes, aeroallergens, and tobacco smoke, is a significant cause of chronic lung inflammation leading to respiratory disease. It is now recognized that resolution of inflammation is an active process controlled by a novel family of small lipid mediators termed "specialized pro-resolving mediators" or SPMs, derived mainly from dietary omega-3 polyunsaturated fatty acids. Chronic inflammation results from an imbalance between pro-inflammatory and pro-resolution pathways. Research is ongoing to develop SPMs, and the pro-resolution pathway more generally, as a novel therapeutic approach to diseases characterized by chronic inflammation. Here, we will review evidence that the resolution pathway is dysregulated in chronic lung inflammatory diseases, and that SPMs and related molecules have exciting therapeutic potential to reverse or prevent chronic lung inflammation, with a focus on lung inflammation due to inhalation of environmental hazards including urban particulate matter, organic dusts and tobacco smoke.

Contents

Abbreviations: AT-RvD1, Aspirin-triggered resolvin D1; BAL, Bronchoalveolar lavage; COPD, Chronic Obstructive Pulmonary Disease; COX2, Cyclooxygenase 2; DEP, Diesel exhaust particles; DHA, Docosahexaenoic acid; DiHOME, Dihydroxyoctadeca(mono)enoic acid; EET, Epoxyeicosatrienoic acid; EOR, Eicosanoid oxidoreductase; EPA, Eicosapentaenoic acid; FPR2, Formyl peptide receptor 2; GPCR, G-Protein coupled receptor; HDHA, Hydroxydocosahexaenoic acid; HDM, House dust mite allergen; HETE, Hydroxyeicosatetraenoic acid; HODE, Hydroxyoctadecadienoic acid; LO, Lipoxygenase; LPS, Lipopolysaccharide; LTA_4, Leukotriene A4; LTB_4, Leukotriene B4; LXA_4, Lipoxin A4; MaR1, Maresin 1; MSC, Mesenchymal stem cell; NSAID, Nonsteroidal anti-inflammatory drug; OVA, Ovalbumin; PD1, Protectin D1; PG, Prostaglandin; PKC, Protein kinase C; PM, Particulate matter; RvD1, Resolvin D1; RvD2, Resolvin D2; RvE1, Resolvin E1; sEH, Soluble epoxide hydrolase; sEHI, Soluble epoxide hydrolase inhibitor; SPM, Specialized pro-resolving lipid mediator; SRE, Serum Response Element; UFP, Ultrafine particulate matter.

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1. Introduction

The adult human lung has an approximate surface area for gas exchange of $100m^2$, about the size of half a standard tennis court, and, resting, inhales and exhales over 10,000 l of air per day (more with exertion). As such, the lung is often the first point of contact and first line of defense for pathogens, particulate matter, dusts and fumes, smoke, and other inhaled environmental toxicants. Tobacco smoking is probably the most widespread intentional inhalation environmental exposure. However, exposure to second hand smoke, wood and biomass smoke, agricultural dust, traffic-related and other forms of air pollution, and other industrial inhalation hazards, also contribute to significant chronic lung inflammation and lung disease (Utell & Samet, 1990). The host inflammatory response evolved to deal with insults such as these, and inflammation is generally a beneficial response. Yet, inflammation must be tightly regulated, as chronic unresolved inflammation causes or contributes to many significant pathologies of its own (Serhan, 2010). It was long assumed that resolution of inflammation was a passive process that occurred when the original stimulus was eliminated, resulting in down-regulation of pro-inflammatory mediators. However, recent research has uncovered a novel family of specialized pro-resolving lipid mediators (SPMs), mainly derived from arachidonic acid and dietary omega-3 polyunsaturated fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) (Chiang & Serhan, 2017; Duvall & Levy, 2016; Serhan, Chiang, & Dalli, 2015). These mediators are critical to self-limited inflammatory responses and there is considerable evidence that chronic inflammation is marked by decreased levels of these mediators. There is also excitement that these molecules represent a new therapeutic opportunity for the many diseases which include chronic inflammation as a pathogenic feature (Serhan & Chiang, 2008). Here, we review emerging evidence that SPMs may represent novel therapies for lung diseases that result from acute and chronic exposures to environmental hazards including tobacco smoking, second hand smoke exposure, air pollution, industrial pollution, and other inhalation hazards.

2. Air pollution, cigarette smoke and other environmental lung insults

This review will examine chronic lung inflammation and inflammatory diseases resulting from environmental lung insults, and the potential for SPMs and other modifiers of the pro-resolution circuitry to moderate and treat lung disease.

Environmental lung insults range from the common (e.g. urban air pollution), to the uncommon (e.g. mine and factory dust, swine dust from commercial feedlot operations) to cigarettes and other forms of tobacco smoking, and come from a variety of sources. Air pollution and other environmental hazards are well-documented to cause acute and chronic lung and cardiopulmonary disease (Sydbom et al., 2001; Thurston et al., 2017). Typical urban air pollution is composed of partially combusted hydrocarbons from vehicle exhaust, gasses such as ozone and nitrogen and sulfur oxides, particulates derived from sand, soil and other local terrestrial sources, and biological materials such as agricultural dust, bacteria and viruses, and aeroallergens such as pollen, mold and house dust mite antigens (Tunno et al., 2018; Zeb et al., 2018). Generally, the particulates of most concern, and that are subject to air pollution regulation, are known as $PM_{2.5}$, particulate matter <2.5 μm in diameter. This is the size threshold to be deposited in the alveoli. Although each inhalation hazard has its own unique chemistry, they can have overlapping constituents and thus, activate pro-inflammatory programming via similar mechanisms.

Black carbon (soot) from combustion sources has a large and highly active surface area and can adsorb materials including metals and hydrocarbons (Long, Nascarella, & Valberg, 2013). Metals, particularly copper and iron, can promote inflammation through generation of reactive oxygen species (Guastadisegni et al., 2010; Harrington, Smirnov, Tsirka, & Schoonen, 2015; Michael, Montag, & Dott, 2013). Polyaromatic hydrocarbons such as naphthalene and anthracene are found in diesel exhaust and other combustion particulates and promote inflammation through upregulation of the aryl hydrocarbon receptor (Awji et al., 2015; den Hartigh et al., 2010; Martey, Baglole, Gasiewicz, Sime, & Phipps, 2005). These inflammatory mechanisms are common to combustion source air pollution including diesel exhaust particulates, urban particulate matter, wood smoke, and biomass smoke. Combustion sources also generate sulfur and nitrogen oxides, which are pro-inflammatory on their own, and which can generate ozone in the presence of sunlight, all of which are potent stimuli of lung inflammation via reactive oxygen species (Muller & Jaspers, 2012; Zielinska, Samy, McDonald, Seagrave, & Committee, 2010).

There are a number of biological sources that contribute to environmental lung injury and that also interact with combustion particles. Agricultural dusts, such as from commercial poultry and swine feeding operations, are strongly pro-inflammatory as well as allergenic. House dust mite and cockroach allergens act in a similar manner. Biological dusts can contain LPS and other microbial pathogen associated molecular patterns (PAMPs), which can cause inflammation via multiple innate immune pathways (Alexis et al., 2006; Poole & Romberger, 2012; Wunschel & Poole, 2016). Agricultural particulate matter also upregulates production of pro-inflammatory eicosanoids including prostaglandins, thromboxanes and leukotrienes by airway epithelial cells (Malireddy et al., 2013). Additionally, these biological insults can interact with combustion products such as urban particulate matter, diesel exhaust, and cigarette smoke, to potentiate the effects of both insults. For example, low dose exposure to diesel exhaust or cigarette smoke can increase the risk of allergic sensitization by aeroallergens (Rumold, Jyrala, & Diaz-Sanchez, 2001; Santos et al., 2014; Sydbom et al., 2001).

Inhalation of air pollution can cause both acute and chronic diseases, including hypersensitivity pneumonitis, acute respiratory distress syndrome, bronchitis, bronchiolitis, and emphysema. This is seen as the result of an imbalance between inflammatory and resolution pathways due to repeated or continued pro-inflammatory stimulation (Balode et al., 2012; Bozinovski et al., 2013; Dudek, Nitzsche, Ludwig, & Ehrhardt, 2016). Although it is not our intention to discuss the immunological basis of asthma in this review, we will discuss the contribution of environmental hazards such as diesel exhaust and aeroallergens to asthma, and how SPMs might be used to treat asthma related to environmental hazards. There are many excellent reviews on the general subject of asthma and SPMs (Duvall, Bruggemann, & Levy, 2017; Levy & Serhan, 2014; Miyata & Arita, 2015; Robb, Regan, Dorward, & Rossi, 2016).

Air pollution also contributes to systemic inflammatory diseases including obesity and cardiovascular disease (Brook, et al., 2010; Moore et al., 2016; Thurston et al., 2017). This is now thought to be caused in part by inhalation of ultrafine particulates (UFP); particulate matter <0.1 μm in diameter. UFP have an active surface area that is orders of magnitude larger than the surface area of an equal mass of $PM_{2.5}$, and generation of UFP is currently unregulated. UFP can cross the alveolar epithelium and endothelium and enter the bloodstream and have effects on distant organs (Utell & Frampton, 2000). UFP increased levels of pro-inflammatory eicosanoids including leukotrienes, prostaglandins and 8-isoprotane relative to anti-inflammatory lipid mediators in both mice and rat alveolar epithelial cells (Beck-Speier, Karg, Behrendt, Stoeger, & Alessandrini, 2012).

An important aspect of air pollution and other environmental hazards is its pervasiveness, as people are exposed whenever they go outdoors (Samet & Utell, 1991). Workers in occupational exposure settings may receive personal protective equipment, but compliance may be haphazard, and non-workers in homes and businesses downwind are still exposed. Government has attempted to limit urban $PM_{2.5}$ by placing emissions controls on pollution sources such as vehicles, powerplant, and even residential lawn mowers and charcoal grills, but urban dwellers are still at the mercy of weather conditions that can cause $PM_{2.5}$ levels vary dramatically from day to day and season to season (Samet & Utell, 1991).

Cigarettes and other forms of tobacco smoking are probably the most common intentional inhalation insult. Tobacco smoke shares similarities with other combustion-sourced pollutants, including carbon particulates, partially combusted hydrocarbons, LPS and other biological products, and gasses such as ammonia (Roemer et al., 2004). Tobacco smoke is well-understood to be a significant cause of diseases including lung cancer and chronic obstructive pulmonary disease (COPD; emphysema, chronic bronchitis and small airway remodeling). In many cases, the severity of COPD continues to worsen, even after smoking cessation, and smoking-related lung inflammation can persist for 10 years or more. As discussed below, this represents, at least in part, a failure of the resolution pathway to self-limit the inflammation caused by smoking, once smoking has ceased.

Tobacco smoking also has direct consequences for non-smokers who are exposed to environmental tobacco smoke (ETS), often referred to as secondhand smoke. ETS is a combination of exhaled mainstream smoke, side stream smoke that burns off the tip of the cigarette between puffs, and smoke particulates that settle on furnishings and remain persistent in the environment. Exposure to ETS is associated with increased risk of respiratory symptoms exposed groups such as flight attendants, and is also associated with increased allergic sensitization and susceptibility to respiratory infection in children who live in a home with a smoker (Beatty, Haight, & Redberg, 2011; Eisner et al., 2005; Gergen, Fowler, Maurer, Davis, & Overpeck, 1998; Goodwin, 2007; Lang, et al., 2013). Tobacco smoking is also a significant added risk factor for disease in people who have occupational exposures to other environmental insults (Khelifi et al., 2014). This suggests that failure to resolve inflammation due to smoke exposure leaves the lungs in a vulnerable state that makes them more susceptible to second insults such as pathogens and aeroallergens.

New therapies for chronic lung inflammatory diseases are urgently needed. Corticosteroids are sometimes used, but chronic use is associated with significant adverse effects; moreover, some asthma and COPD patients become steroid-resistant (Barnes, 2013; Raissy, Kelly, Harkins, & Szefler, 2013). Importantly, corticosteroids do not modify the underlying cause of chronic inflammation, namely an imbalance between pro-inflammatory and pro-resolving pathways that leads to pathologic chronic inflammation. Here, we discuss a newly identified family of endogenous lipid mediators that activate and regulate resolution of inflammation, which are responsible for the typical self-limiting nature of inflammation, and whose disruption is now recognized as a key contributor to chronic inflammation. We also discuss *in vitro* and *in vivo* evidence that these mediators, and the pro-resolution pathway more generally, are an important emerging target for therapeutic intervention.

3. Specialized pro-resolving mediators (SPMs)

"Specialized pro-resolving lipid mediators" (SPMs) describes a family of small lipid molecules derived from endogenous or dietary long chain fatty acids via enzymatic and non-enzymatic reactions. The lipoxins were first reported in 1984 by Serhan and colleagues (Samuelsson, Hammarstrom, Hamberg, & Serhan, 1985; Serhan, Hamberg, & Samuelsson, 1984), with identification of additional DHA and EPA-derived SPMs beginning in 2000 (Serhan et al., 2000). Four main classes of compounds have been extensively studied to date; *lipoxins*, *resolvins*, *protectins* and *maresins* (Schwab & Serhan, 2006; Serhan & Chiang, 2008) (Fig. 1). Most of the SPMs are generated from the dietary omega-3 polyunsaturated fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), although the lipoxins are generated from arachidonic acid, and DHA can be produced in limited quantities *in vivo* through the action of elongation of very long chain fatty acids protein 2 (ELOVL2) (Chiurchiu et al., 2016). Recently, it was discovered that precursors of MaR1, PD1 and RvD1 can form conjugates with small peptides derived from glutathione resulting in MCTRs (maresin conjugates in tissue repair), PCTRs (protectin conjugates in tissue repair) and RCTRs (resolvin conjugates in tissue repair), which have independent biological activity in the repair of tissue injury (Serhan, 2017). Resolvins and lipoxins can be degraded by the enzyme eicosanoid oxidoreductase (EOR, also known as 15-hydroxyprostaglandin dehydrogenase or 15-PGDH) into 8-oxo- and 17-oxo-RvD1, which have significantly reduced biological effect (Clish, Levy, Chiang, Tai, & Serhan, 2000; Sun et al., 2007); while the production of lipoxins can be inhibited by epoxide hydrolases (Flitter et al., 2017; Ono, et al., 2014; Yang et al., 2015). It is plausible that similar enzymes exist to degrade other SPMs, as the resolution pathway is known to be as tightly controlled by feedback mechanisms as inflammatory pathways. SPMs act through a family of G-protein coupled receptors that includes the lipoxin A_4 receptor ALX, also known as formyl peptide receptor 2 or FPR2; the D resolvin receptors (DRV)1 and 2, also known as GPR32 and GPR18 (Chiang, Dalli, Colas, & Serhan, 2015); and the E resolvin receptors (ERV)1 (ChemR23) and BLT1 (Duvall & Levy, 2016). Receptors for other SPMs remain to be identified, and the downstream signaling events are also not well understood at this time (reviewed in (Chiang & Serhan, 2017)). Thus, the status of this pro-resolving signaling network depends on the presence of precursors, synthetic and degrading enzymes, and appropriate GPCRs on target cells.

Also of note is the effect of aspirin on SPM synthesis (Serhan & Chiang, 2008). Aspirin works in part by acetylating COX2, and acetylation changes the stereochemistry of some SPM synthesis reactions. For example, DHA is converted into 7*S*,8*R*,17***S***-trihydroxy-4*Z*,9*E*,11*E*,13*Z*,15*E*,19*Z*-docosahexaenoic acid (RvD1) by the action of 5-lipoxygenase (5-LO) and 15-lipoxygenase (15-LO). However, acetylated COX2 converts DHA into 7*S*,8*R*,17***R***-trihydroxy-4*Z*,9*E*,11*E*,13*Z*,15*E*,19*Z*-docosahexaenoic acid (abbreviated 17*R*-RvD1, aspirin triggered RvD1 or AT-RvD1) (Sun et al., 2007). A similar reaction with arachidonic acid as the parent compound results in AT-LXA_4 rather than LXA_4 (Chiang et al., 1998). AT-LXA_4 can also be formed through cytochrome P450 enzymes that can generate 15*R*-HETE, the precursor to AT-LXA_4, from arachidonic acid (thus, the description of these epimers as "aspirin-triggered" can be a misnomer) (Claria & Serhan, 1995; Keeney et al., 1998). These reactions are significant because the aspirin-triggered forms of the compounds have similar pro-resolving biological activity but are highly resistant to endogenous degradation mechanisms (Sun et al., 2007). This presents a natural example of a modification that increases the compounds' pharmaceutical utility while maintaining activity, and a number of animal model studies discussed below use AT-RvD1 rather than RvD1 for this reason.

SPMs exhibit a variety of anti-inflammatory and pro-resolving properties on numerous cell types. SPMs inhibit production of pro-inflammatory cytokines, downregulate neutrophil activation and migration, and increase non-phlogistic (non-inflammatory) activation of macrophage engulfment and removal of apoptotic inflammatory cells and debris (efferocytosis) (Basil & Levy, 2016). SPMs also inhibit antigen presentation by dendritic cells, promote primary and memory B cell IgG and IgM responses while downregulating allergic IgE production and pro-inflammatory cytokines, and promote differentiation of Tregs while inhibiting Th1, Th2 and Th17 function (Duffney et al., 2018). Importantly, SPMs are pro-resolution without being classically immunosuppressive, and may avoid the side-effects of chronic immune suppression of long-term therapy with corticosteroids and NSAIDs. In fact, by blocking the activity of COX2, NSAIDs have been shown to inhibit production of SPMs as well as inhibiting pro-inflammatory prostaglandins, resulting in delayed resolution of inflammation (Chan & Moore, 2010; Willoughby, Moore, Colville-Nash, & Gilroy, 2000).

Key concepts in understanding the function of SPMs include lipid mediator *class-switching* and *transcellular biosynthesis*. Mediator class-switching describes the phenomenon in which the same cell type switches from producing pro-inflammatory mediators early in inflammation, to producing pro-resolving mediators during the resolution

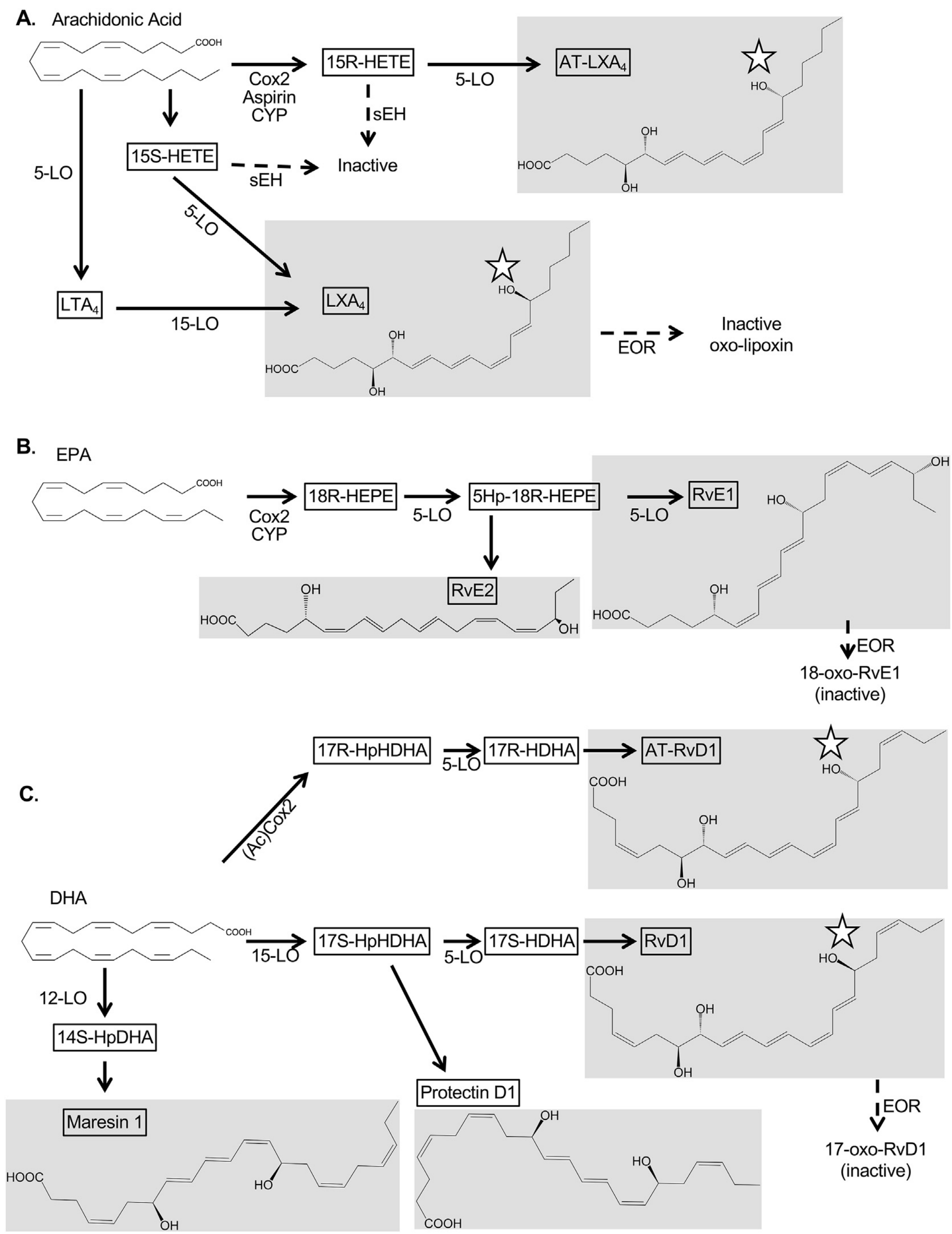

Fig. 1. Diagram of the synthetic pathways for the major classes of SPMs, with selected enzymatic processing steps, final products and degradation pathways. Stars indicate sites at which the aspirin-triggered epimers differ from the standard compound. Abbreviations: (Ac)Cox2, acetylated Cox2; CYP, Cytochrome P450 enzymes; EOR; epoxide oxoreductase; HDHA, hydroxydocosahexaenoic acid; HEPE, hydroxyeicosapentaenoic acid; HETE, hydroxyeicosatetraenoic acid; sHE, soluble epoxide hydrolase. Other abbreviations as defined in the main text.

phase, by altering the expression of key synthetic enzymes to favor SPMs rather than inflammatory mediators. This was first described in a mouse model of air pouch inflammation, in which neutrophils switched from producing leukotrienes to lipoxins by downregulating 5-LO and upregulating 15-LO (Levy, Clish, Schmidt, Gronert, & Serhan, 2001), and has subsequently been demonstrated in human neutrophils, lung fibroblasts, and other cells (Lacy et al., 2016). Transcellular biosynthesis is the observation that some cells only produce SPM precursors but lack the enzymes needed to produce the final SPM; while other cell types can produce the final SPM if provided the precursor (Capra et al., 2015; Serhan et al., 2000). Thus, under normal conditions, SPM biosynthesis is tightly controlled, both spatially and temporally.

Although not classified as SPMs, the epoxyeicosatrienoic acids (EETs) and hydroxyeicosatetraenoic acids (HETEs) are of interest, as they are produced by similar mechanism, and function as indirect precursors of some SPMs in transcellular biosynthesis. EETs are synthesized from omega-6 fatty acids including arachidonic acid via cytochrome P450 epoxygenases, while HETEs are generated by lipoxygenases (LOs) (reviewed in (Capra et al., 2015; Lopez-Vicario et al., 2016; Zeldin, 2001)). HETEs and EETs can serve as precursors of SPMs, and also have potent actions of their own, including regulating inflammatory signaling (Node et al., 1999; Spector, Fang, Snyder, & Weintraub, 2004; Thomson, Askari, & Bishop-Bailey, 2012). As resolvins can be degraded by endogenously produced EOR, EETs can be degraded by endogenous soluble epoxide hydrolases (sEHs), which can promote inflammation by limiting the production of SPMs through reduction in levels of precursors (Liu et al., 2011; Schmelzer et al., 2005; Yang et al., 2015).

SPMs are of significant interest as potential pharmaceuticals (Lee, 2012). Since they are produced endogenously, they are expected to have an excellent safety profile, and the long carbon backbone is amenable to derivatization to increase potency and half-life, reduce local degradation, or to modify its receptor selectivity and mode of action (Serhan & Chiang, 2008). Several clinical trials of dietary supplementation with omega-3 polyunsaturated fatty acids generally, or purified DHA and EPA specifically, have been completed or are underway, albeit with mixed results, as discussed below. Trials of resolvins for psoriasis (NCT03483311) and chronic pain (NCT03095157) are planned or underway, and a trial of an RvE1 derivative for inflammatory dry eye disease has recently completed (NCT00799552). An LXA_4 precursor showed efficacy in a clinical trial in infantile eczema (Wu, Chen, Liu, Wu, & Dong, 2013). The GPCRs through which SPMs signal are also targets for novel small molecule antagonists that would not necessarily need to be derived from SPMs themselves. As the longest-recognized SPM receptor, ALX/FPR2 is farthest along this developmental pathway (Bozinovski et al., 2013; Corminboeuf & Leroy, 2015), while the fact that many SPMs receptors have not yet been identified is an obvious hurdle still to be overcome. Beyond treatment with SPMs themselves, other steps in the pro-resolution pathway offer potential therapeutic targets. For example, lipoxygenase activators may promote SPM production, while selected lipoxygenase inhibitors could enhance production of selected SPMs by blocking production of less desirable SPMs that compete for the same precursor pool. EOR and other enzymes that degrade SPMs are also potential targets for small molecule inhibitors, which would increase the half-life of endogenously produced SPMs (Pillarisetti & Khanna, 2012). Soluble epoxide hydrolase inhibitors (sEHIs) have shown promise in pre-clinical animal models of lung inflammation (Liu et al., 2011; Podolin et al., 2013; Schmelzer et al., 2005; Yang et al., 2015). Pro-resolving circuits can also be targeted with therapeutic micro-RNAs (Fredman, Li, Dalli, Chiang, & Serhan, 2012; Recchiuti, Krishnamoorthy, Fredman, Chiang, & Serhan, 2011; Recchiuti & Serhan, 2012). The effectors of the pro-resolution pathway (SPMs, receptors, key enzymes) represent a fertile area for pharmaceutical development for chronic inflammatory lung diseases that have escaped their endogenous self-limited purpose.

4. SPMs and air pollution: evidence from human studies

Epidemiological and human studies suggest that lipid mediators are markers of exposure to inhaled toxicants and cardiopulmonary diseases. Dysregulated lipid levels are also associated with exposure-related inflammation and diseases. However, studies of dietary supplementation with pro-resolving lipid mediators and precursors, as a preventative or treatment strategy, have revealed mixed results to date.

Increased levels of inflammatory lipid mediators are associated with the inhalation of air pollution. Oxylipins that promote airway inflammation, including 12,13-DiHOME, 9-HODE, 5-HETE, and 13-HODE, are increased in the plasma and bronchoalveolar lavage (BAL) fluid of adults up to 24 h after an acute exposure to biodiesel exhaust or subway air (Gouveia-Figueira et al., 2017; Gouveia-Figueira et al., 2018; Lundstrom et al., 2011). 8-isoprostane, an indicator of oxidative stress that is derived from arachidonic acid, is increased in people exposed to air pollutants. 8-isoprostane is also elevated in the exhaled breath condensate of children exposed to black carbon particulate matter and in the urine of individuals exposed to wood smoke from cooking fires (Allen et al., 2011; Barregard et al., 2006; Commodore et al., 2013; Patel, Chillrud, Deepti, Ross, & Kinney, 2013). Similarly, another marker of lipid peroxidation, urinary 8-epi-prostaglandin $F_{2\alpha}$, is increased in individuals after short-term exposure to fine particulate matter (W. Li et al., 2016). Even prenatal exposures to particulate matter have been correlated with increased levels of inflammatory lipoxygenase metabolites, such as 5-HETE, 9-HODE, and 15-HETE, in neonatal cord blood (Martens et al., 2017). Increased inflammatory lipid levels in people are associated with the inhalation of pollutants and inflammatory diseases related to air pollution.

Asthma, an inflammatory allergic airway disease, is associated with increased concentrations of 8-isoprostane and decreased levels of pro-resolving LXA_4 in blood, sputum, and bronchoalveolar lavage fluid (Duvall & Levy, 2016; Ono, et al., 2014). This disease is associated with increased bronchoalveolar lavage levels of prostaglandin $(PG)D_2$, which causes bronchoconstriction (Fajt et al., 2013). Inflammatory cysteinyl leukotrienes derived from arachidonic acid are also elevated while protectin D1 (PD1) is reduced in the exhaled breath condensate of asthmatics (Duvall & Levy, 2016; Levy et al., 2007; Linares Segovia et al., 2014). Similarly, increased arachidonic acid levels and decreased DHA was found in the nasal scrapings of people with asthma (Freedman et al., 2004). Inflammatory lipid mediators are correlated with airway inflammation.

As tobacco smoking in various forms is the most common form of intentional exposure to “air pollution,” there is considerable interest in the effects of smoking on pro-inflammatory and pro-resolving lipids. For example, RvD1 is decreased, while 17-HDHA, 14-HDHA, 12-HETE, and 15-HETE are increased, in the BAL of individuals with COPD (Croasdell et al., 2015). Similarly, patients with COPD exhibit increased leukotrienes and decreased LXA_4 in BAL and sputum, suggesting an imbalance between pro-inflammatory and pro-resolving pathways (Balode et al., 2012; Duvall & Levy, 2016). Serum amyloid A is a pro-inflammatory mediator that binds to the ALX/FPR2 receptor and opposes the pro-resolving effects of LXA_4 which acts through the same receptor. Serum amyloid A was detected in the serum and BAL fluid of COPD patients, and was dramatically increased relative to LXA_4 during acute exacerbations of COPD (Bozinovski et al., 2012), consistent with the hypothesis that smoking results in an imbalance between inflammation and resolution. Smokers with COPD also have higher serum levels of monounsaturated fatty acids and lower levels of omega 3 fatty acids compared to nonsmokers (Titz et al., 2016). Increased PGE_2 is also present in the sputum and exhaled breath condensate and increased serum amyloid A, which can bind to and block ALX receptors, is increased in the BAL of COPD patients (Duvall & Levy, 2016; Zaslona & Peters-Golden, 2015). Our own work with lung lipid mediators in cigarette smoking is summarized in Fig. 2. We found that RvD1 is decreased in BAL and serum from COPD patients relative to healthy nonsmokers (Croasdell et al., 2015). Intriguingly, expression of eicosanoid oxidoreductase (EOR), was increased in lung tissue of COPD patients (Hsiao et al., 2015), suggesting a possible explanation for diminished RvD1 levels (Fig. 2C). Although we are not directly considering respiratory infections in this review, it is worth noting that individuals with cystic fibrosis exhibit reduced lung levels of omega 3 fatty acids and lipoxins (Eickmeier et al., 2017; Karp et al., 2004), and that *Pseudomonas aeruginosa*, a key pathogen in cystic fibrosis, expresses an epoxide hydrolase as a virulence factor. This enzyme hydrolyzes anti-inflammatory EETs including the lipoxin precursor 14,15-EET, inhibiting the production of pro-resolving lipoxins (Flitter et al., 2017). Thus, induction of SPM-destroying enzymes as a pro-inflammatory response has been adopted as an evolutionary strategy by at least one significant pathogen. Taken together, our results along with others show that inhalation of cigarette smoke, diesel exhaust, and other inhalation insults, both acutely and chronically, can depress normal endogenous resolution signals in the lungs.

Similarly, a Western high fat diet with arachidonic acid is associated with an increased risk for cardiovascular disease. Higher circulating levels of DHA and EPA in individuals are inversely correlated with cardiovascular disease (Superko et al., 2014). Higher serum concentrations of arachidonic acid and reduced levels of RvD1 are also detected in symptomatic patients with carotid disease (Bazan et al., 2017). People with CVD also have increased circulating levels of 8-isoprostane.

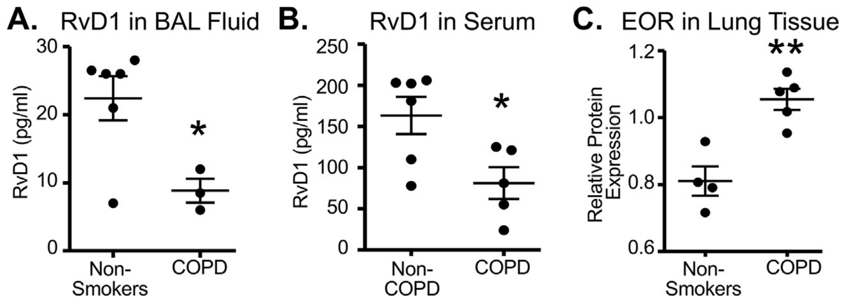

Fig. 2. RvD1 is decreased in COPD patients. Panels A and B: RvD1 was measured in bronchoalveolar lavage fluid (BAL) and serum from non-smokers without COPD and from COPD patients by EIA as previously reported (Croasdell et al., 2015). Panel C: Levels of eicosanoid oxidoreductase (EOR), an enzyme that degrades and inactivates RvD1, were measured in lung tissue from non-smoking donors or COPD patients, as previously reported (Hsiao et al., 2015).

Evidence of the efficacy of supplementation with omega-3 polyunsaturated fatty acids is mixed. A recent controlled trial of fish oil supplementation found a significant reduction in wheeze, asthma, and respiratory infections in 3 year old children whose mothers received fish oil during the third trimester (Bisgaard et al., 2016), while similar trials showed that prenatal omega-3 supplementation increased the levels of DHA and reduced allergic responses in infants (D'Vaz et al., 2012; Miyake, et al., 2007). However, two other trials found no difference in allergic sensitization in children after pre-natal fish oil supplementation at 6 years of follow up (Best et al., 2016; Best et al., 2018). A systematic review of diet and air pollution found that a Mediterranean diet high in omega-3 fatty acids was associated with reduced airway disease in smokers and people exposed to air pollution, but there was insufficient data that omega-3 fatty acid supplementation was protective against the effects of exposure to air pollution other than tobacco smoke (Whyand, Hurst, Beckles, & Caplin, 2018).

There have been a number of observational studies and clinical trials examining omega-3 fatty acid supplementation in individuals with COPD, also with mixed results. A recent placebo-controlled feasibility trial discovered challenges in recruitment participant retention, and adherence to the supplement protocol for studies of omega-3 supplementation in COPD patients (Fulton et al., 2017). A longitudinal and a cross-sectional retrospective study, which determined DHA and EPA intake through patient-reported dietary information, found no association between omega-3 fatty acid consumption and COPD (McKeever et al., 2008; Tabak et al., 1998). Similarly, a prospective cohort study also found no association between diets reported to have higher amounts of omega-3 fatty acid foods and COPD mortality (Walda et al., 2002). However, intake of omega-3 fatty acids by participant recall was inversely correlated with COPD in a prospective case-control study and a cross-sectional study (Ahmadi, Haghighat, Hakimrabet, & Tolide-ie, 2012; de Batlle, et al., 2012). Increased dietary omega-3 fatty acids were also associated with a decreased risk for COPD in the Nurses' Health Study and lowered serum levels of inflammatory markers. In addition to dietary information, greater blood levels of EPA but not DHA were associated with inflammatory markers and COPD in prospective studies (De Castro et al., 2007; Novgorodtseva et al., 2013). Recent systematic meta-analyses report inconclusive evidence to support the hypothesis that omega-3 fatty acid supplementation reduces the risk of COPD (Atlantis & Cochrane, 2016; Fulton, Hill, Williams, Howe, & Coates, 2015).

There is currently an ancillary study of a clinical trial in progress examining the effects of omega-3 fatty acid supplementation on COPD outcomes and exacerbations (Gold et al., 2016). One of primary aims of this clinical trial (NCT01169259) and the OMEGA-SPM-DOSE study (NCT02719665) are to determine if omega-3 supplementation affects cardiovascular disease. This is an important research question since, similar to COPD, mixed results have been found with omega fatty acid intake and cardiovascular disease outcomes. Meta-analyses and studies have reported that omega-3 fatty acid supplementation did not reduce the risk for cardiovascular disease events or markers of oxidative stress and inflammation (Tenenbaum & Fisman, 2018). Yet, a recent meta-analysis of randomized controlled trials found that omega-3 fatty acids reduced inflammatory cytokines and improved vascular dysfunction in patients with coronary artery disease (Tenenbaum & Fisman, 2018). It's thought that these variable results may be due in part, to differences in the dose of omega-3 fatty acid supplementation (Tenenbaum & Fisman, 2018). Additionally, a recent study found that higher serum levels of DHA and EPA were correlated with lower fibrinogen levels in patients exposed to ambient air pollution (Croft et al., 2018). Similarly, omega-3 fatty acid supplementation was found to be protective against particulate matter-related cardiac function abnormalities (Peter et al., 2015). There are variable data about the effects of omega-3 fatty acids and pro-resolving lipid mediators on cardiovascular disease.

Human studies show that inflammatory and pro-resolving lipid mediators could be potential biomarkers of exposure to air pollutants, as well as contribute to toxicant-related diseases. However, more clinical studies are needed to understand the effects of supplementing pro-resolving lipid mediators on toxicant-associated inflammatory lung diseases and respiratory infections. However, recent experimental studies provide strong evidence that pro-resolving lipid mediators may be effective therapies against pollutant induced-lung inflammation.

5. *In vitro* investigations in lung and airway cells

Many important insights into the use of SPMs are potential therapies for environmental exposure driven lung disease have been obtained from *in vitro* studies of lung cells exposed to inflammatory stimuli (Table 1). Here, we consider epithelial cells as first point of contact with inhaled insults, macrophages as a key line of defense which act to engulf and remove inhaled particulate matter, and fibroblasts and other mesenchymal cells.

5.1. Epithelial cells

Lung airway epithelial cells are critical to maintaining airway homeostasis and are often the first responders to exposures (Muller & Jaspers, 2012). Several studies have revealed that diesel exhaust particles (DEP) alter lipid mediator production in epithelial cells. A549 cells, a transformed alveolar epithelial cell line, was exposed to DEP, and COX-2 and PGE_2 production were measured (Ahn et al., 2008). DEP lead to a dramatic increase in both COX-2 expression and production of its downstream metabolite, PGE_2. In a more recent study, immortalized human bronchial epithelial cells were exposed to DEP for either acute or long-term periods (Rynning et al., 2018). Short term exposure to DEP induced production of both PGE_2 and $PGF_{2\alpha}$. Interestingly, the epithelial cells exposed to long term DEP showed a more fibroblast like morphology, expressed mesenchymal markers such as vimentin and released increased levels of PGE_2 and $PGF_{2\alpha}$ even after DEP was removed, though levels of LXA_4 and HETE metabolites remained unchanged. This suggests DEP is able to transform these epithelial cells

Table 1
In vitro studies of SPMs in lung cells suggesting therapeutic potential.

Lipid/Lipid modifier	Targets	Mechanism	Cell types reported	Reference
EPA, DHA		Increased production of pro-resolution lipid mediators; increases recellularization of lung scaffolds	MSCs, lung fibroblasts, epithelial cells and monocytes	(Abreu et al., 2018; Nordgren et al., 2014; Nordgren, Heires, et al., 2018)
RvD1 and AT-RvD1	GPR32, ALX/FPR2	Reduce inflammatory cytokines, increase macrophage phagocytosis and M2 phenotype, reduce NF-κB, STAT6, STAT1, TAK1, TBK signaling	Macrophages, Lung fibroblasts, bronchial epithelial cells, small airway epithelial cells	(Croasdell et al., 2015; de Oliveira et al., 2017; Hsiao et al., 2013; Hsiao et al., 2014)
RvD2	GPR32, ALX/FPR2	Reduce inflammatory cytokines, increase phagocytosis in macrophages exposed to cigarette smoke extract	Macrophages	(Croasdell et al., 2015)
MaR1	Serum Response element signaling	Reduction of IL-6 and IL-8, lowered neutrophil accumulation, IL-6 and TNFα levels in BAL	Bronchial epithelial cells	(Nordgren et al., 2013)
Protectin		Increased differentiation of macrophages, increased efferocytosis/phagocytosis	Monocytes, macrophages	(Pistorius et al., 2018)
Soluble epoxide hydrolase inhibitors (sEHIs)	Soluble epoxide hydrolase	Reduced breakdown of pro-resolution lipid mediators	*Ex vivo* analysis of human and rodent blood, serum, sputum and BAL cells	(Ono, et al., 2014; Podolin et al., 2013).

Abbreviations: AT-RvD1, aspirin-triggered resolvin D1; BAL, bronchoalveolar lavage; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MaR1, maresin 1; MSC, mesenchymal stem cells or mesenchymal stromal cells; RvD1, resolvin D1; RvD2, resolvin D2; sEHI, soluble epoxide hydrolase inhibitor

into a more pro-inflammatory cell type that may increase susceptibility and immunomodulation to promote allergic asthma and COPD (Rynning et al., 2018). Mechanistically, wood smoke enhanced cigarette smoke-induced inflammation in human airway epithelial cells by blocking LXA_4 production (Awji et al., 2015), while RvD1 inhibited IL-8 production and NF-κB activation in human bronchial epithelial cells (Dong et al., 2014).

House dust mite allergen includes both bacterial LPS and allergenic dust mite proteins, the combination of insults provokes strong inflammatory responses from airway epithelial cells and can cause airway inflammation and asthmatic symptoms. Both RvD1 and AT-RvD1 significantly reduced inflammatory cytokine production in bronchial epithelial cells with associated reductions in NF-κB, STAT6 and STAT1 signaling (de Oliveira, da Silva, & Rogerio, 2017). This study also confirmed that the effects of RvD1 were dependent upon the known RvD1 receptor, FPR2/ALX, as had previously been reported for LXA_4 (Bonnans, Fukunaga, Levy, & Levy, 2006; Bozinovski et al., 2012).

Airborne agricultural particular matter (PM) from poultry dust can also increase respiratory tract inflammation, common in agricultural workers. Respiratory epithelial cells exposed to agricultural PM produced increased levels of prostaglandins, thromboxane A_2 and leukotrienes B_4 and C_4 (Malireddy et al., 2013). Testing therapeutic uses of SPMs, several studies show that adding SPMs to cell cultures limits inflammatory responses from agricultural organic dust exposure in bronchial epithelial cells. MaR1 dose dependently reduced IL-6 and IL-8 production in bronchial epithelial cells exposed to swine dust (Nordgren et al., 2013). Mechanistically, MaR1 appears to act by limiting protein kinase C (PKC) and Serum Response Element (SRE) transcriptional activity while not inhibiting other inflammatory signaling pathways such as NF-κB and AP-1 signaling. Another study by the same group showed that epidermal growth factor receptor (EGFR) signaling is disrupted in both human bronchiolar epithelial cells and in mice exposed to agricultural dust extract, while DHA supplementation increased EGFR signaling in both *in vitro* and *in vivo* models following dust exposure (Nordgren et al., 2018). EGFR signaling is an important regulator of repair pathways in airway epithelial cells after injury. While DHA appears to increase production of the EGFR ligand, amphiregulin to increase signaling, it not clear how the omega-3 fatty acid signals in this context. These studies show that respiratory tract epithelial cells can respond to environmental insults through alterations in lipid mediator production.

5.2. Macrophages

Macrophages are key cells that coordinate the response to exposure related lung disease. Macrophages, derived from monocytes, aid in clearance of apoptotic cells, cell debris and foreign bodies. Air pollutants including cigarette smoke and diesel exhaust particulates promote production of inflammatory mediators including pro-inflammatory lipids like leukotrienes and prostaglandins via the COX2/arachidonic acid pathway. Rat alveolar macrophages exposed to DEP showed increased expression of COX2 and a concomitant increase in PGE_2 production (Bhavaraju et al., 2014). LPS, a powerful inflammatory stimulant and inducer of COX-2 on its own, could be further pushed to induce COX-2 expression in human monocytes with the presence of DEP (Hofer et al., 2004). These studies went further to show that DEP could further enhance other pathways that induce COX-2 in human monocytes including activation with the Toll-like receptor 2 (TLR2) ligand, Pam3Cys. Additional studies have shown a prominent COX-2 response in macrophages when they are cultured with airborne particulate matter. RAW 264.7 mouse macrophages were exposed to air pollution particulate matter which caused large increases in oxidative stress and PGE_2 production (Schneider, Card, Pfau, & Holian, 2005). Addition of glutathione, a powerful antioxidant was able to prevent the particulate matter's ability to increase PGE_2 levels. Agglomerates of ultrafine particles that contain carbon and titanium dioxide also induce changes in lipid mediators in alveolar macrophages. Canine macrophages exposed to ultrafine particles produced high levels of PGE_2 and LTB_4 (Beck-Speier et al., 2001). Alveolar macrophages are also a major source of the pro-inflammatory leukotriene, LTB_4. LTB_4 is elevated in asthmatics and recent work suggests that phthalate exposure is linked to LTB_4 levels. A recent study showed that primary rat alveolar macrophages exposed to mono(2-ethylhexyl) phthalate produced elevated levels of LTB_4 through phthalate induced ROS formation and the 5-LO pathway (Rakkestad, Holme, Paulsen, Schwarze, & Becher, 2010). Macrophages are a key effector cell and can respond robustly to a variety of environmental and pharmacological exposures.

Several studies show the importance of SPMs in this pathway. For instance, a recent study reported that the protectin metabolic pathway regulates human monocyte to macrophage differentiation and macrophage function (Pistorius et al., 2018). The authors showed that inhibition of protectin synthesis in human and mouse monocytes led to a loss of macrophage differentiation and a dramatic reduction in efferocytosis and bacterial phagocytosis. Thus, a deficiency in protectin or protectin precursors leads to a loss of functional macrophages and likely prevents resolution of inflammation. Another recent study also showed macrophages can also produce maresins such as 13S,14S-epoxy-maresin (13,14-eMar) and MaR1, derived from DHA (Dalli et al., 2013). 13,14-eMaR was shown to be a pro-resolution SPM by blocking LTA_4 hydrolase and by promoting conversion of pro-inflammatory M1 macrophages to the pro-resolving M2 phenotype. In addition to protectins and maresins, RvD1 and RvD2 have been shown by our group to play an important role in pro-resolving macrophage function. RvD1 and RvD2 attenuated spontaneous release of pro-inflammatory cytokines including IL-8 and TNFα by BAL macrophages from COPD patients, while increasing their capacity to phagocytose labeled bacteria (Croasdell et al., 2015). RvD1 and RvD2 had the same effect on monocyote derived macrophages exposed to cigarette smoke extract *in vitro*, as well as reducing the carbonylation of cytoplasmic proteins, a marker of oxidative stress. The resolvins acted by dampening NF-κB activation in a receptor-mediated mechanism (Croasdell et al., 2015; Hsiao et al., 2013). There appears to be a fine balance between production of lipid mediators based on the protective/resolving COX and pro-inflammatory LO pathways (namely PGE_2 and LTB_4, respectively). When pro-inflammatory LO pathways overtake the other side, serious lung disease can result.

5.3. Mesenchymal cells, fibroblasts and other lung cells

Mesenchymal stem/stromal cells (MSCs) are another key player in lung repair and resolution processes. A recent study on human lung MSCs shows that agricultural waste products disrupt lipid mediator signaling (Nordgren, Bailey, Heires, Katafiasz, & Romberger, 2018). Agricultural organic dust is an important exposure that triggers airway inflammation and it has been implicated in the increase in lung disease observed in agricultural workers. In the study, MSCs were stimulated with dust extract obtained from swine containment facilities. Exposed MSCs produced more inflammatory mediators such as TNFα, IL-6 and IL-8 as well as increased production of resolving molecules such as RvD1. These studies suggest lung resident MSCs are a source of pro-resolution molecules that are important in response to environmental exposures (Nordgren, Bailey, et al., 2018). Although this report did not identify specific functional mediators, a previous study in an LPS-induced acute lung injury model reported that the protective effect of MSCs was conveyed by LXA_4 (Fang et al., 2015). In studies by our group, primary human lung fibroblasts, small airway epithelial cells and blood monocytes were exposed to cigarette smoke extract, which increased pro-inflammatory responses including IL-6 and IL-8. Remarkably, RvD1 attenuated this proinflammatory signaling in all three cell types (Croasdell et al., 2015; Hsiao et al., 2013). Interestingly we also found that lung fibroblasts treated with cigarette smoke extract produced both pro-inflammatory and pro-resolving mediators in a temporally regulated manner (Lacy et al., 2016). At day 1–2 after treatment with cigarette smoke extract, lung fibroblasts expressed increased COX2 and produced pro-inflammatory mediators including IL-6 and PGE_2; however, at later time points, COX2 expression and PGE_2 production waned and was replaced by production of anti-inflammatory prostaglandins including ligands for peroxisome proliferator-activated receptor γ (PPARγ). This is consistent with other studies showing that cells can produce both pro-inflammatory and pro-resolving mediators in a temporally regulated manner; responding to the inflammatory insult at first but with the capacity to limit their own inflammatory responses to prevent them from becoming pathogenic.

Few studies have examined the response of primary neutrophils to air pollution *in vitro*. One recent study showed neutrophils are readily activated by DEP exposure (Matsuzaki et al., 2006). DEP induced IL-8, LTB_4 and MMP-9 production in neutrophils demonstrating that activated neutrophils contribute to DEP-mediated chronic inflammatory lung diseases. There is ample evidence in other inflammatory models that neutrophils contribute to both the pro-inflammatory and pro-resolving environment, and that they can both produce and respond to SPMs to enhance resolution of inflammation (reviewed in (Jones, Robb, Perretti, & Rossi, 2016)). And, as discussed below, there is strong evidence for neutrophil involvement in therapeutic studies of SPMs in animal models of exposure to smoke and other inhalation insults.

6. Insights from animal models including therapeutic trials

Promising *in vitro* results combined with *in vivo* studies of pro-inflammatory and pro-resolving responses in lung inflammatory lung disease models suggest that SPMs have important therapeutic potential in chronic lung disease.

The majority of studies of SPMs in animal models of lung disease to date involve mouse models of allergic airways disease or asthma, usually initiated by model allergens such as ovalbumin (OVA) or house dust mite allergen. These studies have been comprehensively reviewed elsewhere (Barnig, Frossard, & Levy, 2018; Duvall & Levy, 2016; Miyata & Arita, 2015). Briefly, there is strong evidence that SPM production is attenuated in allergic airways disease, including reductions in maresins, lipoxins, protectins and resolvins, consistent with reports from human studies (Bilal et al., 2011; Kolmert et al., 2018; Krishnamoorthy et al., 2015; Pyrillou, Chairakaki, Tamvakopoulos, & Andreakos, 2018). Different models show distinct SPM profiles, although whether this is due to differences in the antigen response or detection method, remains unclear.

A few studies to date have looked at the involvement of SPMs in asthma as exacerbated by different forms of air pollution. Ambient ultrafine particulate matter (UFP) is a well-documented risk factor for both cardiovascular and respiratory diseases. UFP inhalation induces oxidative stress in the lung that may contribute to allergen-induced lung inflammation (Beck-Speier et al., 2001). UFP exposure in OVA-allergen challenged mice significantly increased production of both inflammatory (LTB_4, 8-isoprostane) and anti-inflammatory/pro-resolving lipid mediators (LXA_4, 15-HETE and PGE_2) in the lung (Beck-Speier et al., 2012). While both pro inflammatory and pro-resolution molecules were induced, UFP tips the balance towards inflammatory signals creating a more robust allergen response to OVA. Thus, an imbalance of lipid mediator signaling may be a root cause of the increased susceptibility of asthma patients to particulate matter. Another recent study investigated whether or not airborne UFP exposure alters fatty acid metabolism and lipid mediator production in the gut (R. Li et al., 2015). Mice lacking the LDL receptor were exposed to UFP or filtered air for 10 weeks in a chronic exposure model. The authors first measured lipid mediators present in the small intestine. Several lipid mediators including: 15-HETE, 12-HETE, 5-HETE and PGD_2 were upregulated in response to UFP. This result suggests that UFP, like $PM_{2.5}$ impacts inflammatory signaling through altering lipid mediator production.

Wood smoke is another combustion-derived source of ambient air pollution, and chronic exposure is associated with bronchitis, respiratory infection, and lung cancer. In mice, wood smoke exposure induces neutrophilic inflammation similar to cigarette smoke, including significant decreases in LXA_4 (Awji et al., 2015). Interestingly, wood smoke also synergized with cigarette smoke to cause greater inflammation and suppression of LXA_4 than either insult alone. LXA_4 is also implicated in a guinea pig model of chronic bronchitis following cigarette smoke exposure. Cigarette smoke exposure alone significantly suppressed LXA_4 in BAL fluid. Treatment with naringin, a flavanone extracted from citrus fruits, reversed the pro-inflammatory effects of smoke exposure, including inflammation, goblet cell hyperplasia and TNFα production, and also restored normal levels of LXA_4 (Luo et al., 2012). Overall, the evidence supports the conclusion that inhalation of combustion-derived air pollution disrupts the balance of inflammatory and resolution pathways in a profoundly pro-inflammatory way.

Many SPMs and SPM precursors that may aid in resolving lung disease have been investigated in preclinical animal models, using both dietary supplementation with DHA and EPA, or with direct therapeutic administration of specific purified SPMs. In rodent models of allergic airways inflammation or asthma, therapeutic efficacy has been demonstrated for LXA_4, LXB_4, MaR1, RvE1, RvD1, PD1 and fish oil dietary supplementation (Duvall & Levy, 2016; Flesher, Herbert, & Kumar, 2014; Ishizuka, Hisada, Aoki, & Mori, 2008; Karra, Haworth, Priluck, Levy, & Levi-Schaffer, 2015; Krishnamoorthy et al., 2015; Levy et al., 2007; Navarro-Xavier et al., 2016; Rogerio et al., 2012). Pre-treatment of MSCs with EPA enhanced their ability to resolve lung inflammation after sensitization and challenge with house dust mite allergen (Abreu et al., 2018). The importance of LXA_4 was further illustrated by a study using an inhibitor of leukotriene A_4 hydrolase (LTA_4H), the enzyme responsible for production of the proinflammatory LTB_4. The LTA_4H inhibitor attenuated allergic airway hyperresponsiveness in mice, which was accompanied by dramatically increased levels of LXA_4, possibly due to shunting of precursors to the lipoxin pathway (Rao et al., 2010).

Studies examining the efficacy of SPM in animal models of lung disease due to air pollution and other inhaled insults are summarized in Table 2. To date there are few published studies examining the efficacy of SPMs in asthma models exacerbated by air pollution. One such study investigated the effects of urban particulate matter (PM), which is hypothesized to have contributed to the rapid increase in the number of people with asthma. In the OVA model of allergic asthma in mice, co-exposure to urban $PM_{2.5}$ significantly increased lung inflammation, BAL cell counts, and the Th2 cytokines IL-5, IL-13 and IL-33. Treatment with LXA_4 significantly attenuated the effect of urban PM by reducing BAL cell infiltrates, tissue inflammation, Th2 cytokines, and dampening expression of the key Th2 transcription factors RORα and GATA3 (Lu et al., 2018).

As mentioned above, agricultural waste dust extract can promote inflammatory signaling in cell culture systems. Animal studies in which mice are exposed to dust extract by intranasal challenge also show high levels of airway inflammation and neutrophil accumulation. Dietary supplementation with DHA reduced neutrophilic infiltration, pro-inflammatory cytokines, and inflammation, in mice challenged intranasally with dust from a commercial swine operation (Nordgren et al., 2014). The investigators then tried purified MaR1, one of the downstream products of DHA metabolism, and which had previously reduced inflammatory cytokine production in bronchial epithelial cells exposed to agricultural dust (Nordgren et al., 2013). MaR1 lowered BAL neutrophils, IL-6 and TNFα levels in mice exposed both acutely and chronically to agricultural dust, but did not reduce histological inflammation (Nordgren et al., 2015). This suggested that MaR1 may only target some of the mechanisms of swine dust induced inflammation and that other DHA metabolites might also play important roles. While both lipid mediators proved useful, a difference in administration may prove advantageous for DHA, which was successfully delivered orally while MaR1 was given intraperitoneally. Interestingly, as opposed to many other studies on SPM mechanisms of action, MaR1 did not block NF-κB signaling, rather, it attenuated serum response element signaling in bronchial epithelial cells exposed to dust extract (Nordgren et al., 2013). It is also possible these mediators influence EGFR signaling to promote successful resolution. Whether this mechanism is responsible for the *in vivo* effects of DHA and MaR1 are currently unknown. Dietary supplementation with omega-3 polyunsaturated fatty acids containing DHA was also effective at reducing symptoms of chronic respiratory disease in horses on a low-dust diet (Nogradi, Couetil, Messick, Stochelski, & Burgess, 2015).

Smoking is the most well-known risk factor for development of emphysema and COPD. Cigarette smoke exposure in animal models causes acute inflammation with neutrophilia and increased pro-inflammatory cytokines. Evidence that smoking promotes an imbalance between pro-inflammatory and pro-resolving pathways that is centered around ALX/FPR2 (the LXA_4 and RvD1 receptor) was recently reviewed (Bozinovski et al., 2013). Thus, several recent studies have examined RvD1 in mouse models of cigarette smoke exposure. AT-RvD1 given concurrently with cigarette smoke exposure for 3 days significantly blunted acute inflammation, neutrophil recruitment, and pro-inflammatory signaling (Hsiao et al., 2013). Importantly, AT-RvD1 given after the final smoke exposure accelerated the resolution of inflammation (Hsiao et al., 2013). Chronic exposure to cigarette smoke in rodent models leads to emphysematous changes including airspace

Table 2
Therapeutic uses of SPMs in animal models of lung disease influenced by air pollution and smoking exposures.

Lipid/Lipid Modifier	*In vivo* model	Result	Reference
EPA	Allergic airways inflammation to house dust mite antigen	MSCs pre-treated with EPA suppressed inflammation and produced elevated levels of SPMs	(Abreu et al., 2018)
DHA	Instillation of agricultural dust	Dietary DHA reduced BAL neutrophil influx and pro-inflammatory cytokines	(Nordgren et al., 2014)
DHA	Instillation of agricultural dust	Mice on a high-DHA diet were protected from inflammation and exhibited increased levels of the repair protein amphiregulin	(Nordgren, Heires, et al., 2018)
Omega-3 PUFA	RCT of omega-3 PUFA supplementation in horses with chronic respiratory disease	Supplementation increased plasma levels of DHA and significantly reduced clinical symptoms compared to a low-dust diet alone	(Nogradi et al., 2015)
MaR1	Instillation of agricultural dust	Pretreatment with MaR1 by i.p. injection attenuated tissue inflammation, BAL neutrophil influx, and pro-inflammatory cytokine production	(Nordgren et al., 2015)
RvD1	Acute cigarette smoke exposure	RvD1 given by inhalation reduced cigarette smoke-induced inflammation, and accelerated resolution of inflammation when given after smoking cessation	(Hsiao et al., 2013)
AT-RvD1	Chronic cigarette smoke exposure	AT-RvD1 given by inhalation or i.v. injection inhibited emphysematous changes in lung architecture, and reduced lung inflammation, oxidative stress and apoptosis	(Hsiao et al., 2015)
RvD1	Chronic cigarette smoke exposure	RvD1 inhibited structural emphysema and inflammation when given concurrently with smoke exposure, and promoted lung tissue regeneration when given after smoking cessation	(Kim et al., 2016)
AT-RvD1	Chronic cigarette smoke exposure	AT-RvD1 promoted tissue repair by upregulating the Nrf2/Keap1 pathway	(Posso et al., 2018)
LXA_4	Urban particulate matter exacerbation of allergic airway inflammation (asthma)	LXA_4 inhibited tissue inflammation, BAL eosinophils, Th2 cytokines, and expression of Th2 transcription factors	(Lu et al., 2018)
Soluble epoxide hydrolase inhibitor (sEHI) *t*-TUCB	Mouse OVA model of allergic airway inflammation	*t*-TUCB increased tissue levels of anti-inflammatory EETs and reduced inflammation, eosinophils and Th2 cytokines	(Yang et al., 2015).
sEHI GSK2256294A	Acute cigarette smoke exposure	GSK2256294A inhibited BAL neutrophilia and lung tissue CXCL1	(Podolin et al., 2013).

Abbreviations: AT-RvD1, aspirin-triggered resolvin D1; BAL, bronchoalveolar lavage; DHA, docosahexaenoic acid; EET, Epoxyeicosatrienoic acids; EPA, eicosapentaenoic acid; LXA_4, lipoxin A_4; MaR1, maresin 1; MSC, mesenchymal stem cells or mesenchymal stromal cells; PUFA, polyunsaturated fatty acids; RCT, randomized controlled trial; RvD1, resolvin D1; RvD2, resolvin D2; sEHI, soluble epoxide hydrolase inhibitor; *t*-TUCB, trans-4-{4-[3-(4-Trifluoromethoxyphenyl)ureido]cyclohexyloxy}benzoic acid.

enlargement, cellular inflammation, neutrophil activation, and oxidative stress. Our group showed that RvD1 prevented airspace enlargement and reduced macrophage and neutrophil infiltration in mice exposed chronically to cigarette smoke (Hsiao et al., 2013). AT-RvD1 reduced production of pro-inflammatory cytokines IL-6 and Cxcl1, inhibited expression of COX2 and ICAM1, and induced the anti-inflammatory cytokine, IL-10. RvD1 also promoted differentiation of alternatively activated (M2) macrophages and neutrophil efferocytosis while reducing lung cell apoptosis. Subsequently, Posso et al. demonstrated that AT-RvD1 enhanced resolution and repair in mice when given after smoking cessation. AT-RvD1 reduced oxidative stress by upregulating the Nrf2 pathway, increased IL-10 expression, and promoted restoration of lung elastin fibers (Posso et al., 2018). In a third study, RvD1 given for 6 weeks after smoking cessation (regeneration model) had the same beneficial effect as RvD1 given during the final 6 weeks of smoke exposure (prevention model) (Kim et al., 2016).

In addition to testing SPMs as direct treatments, research is progressing to target other key enzymes in the SPM pathways. As discussed above, soluble epoxide hydrolases (sEHs) sEH promote inflammation by degrading lipid mediators and precursors derived from arachidonic acid, EPA and DHA, and soluble epoxide hydrolase inhibitors (sEHIs) have been proposed as treatments for inflammatory diseases by inhibiting degradation of anti-inflammatory EETs. A recent study tested an sEHI in the mouse OVA model of allergic airways inflammation (Yang et al., 2015). Inhibition of sEH reduced BAL eosinophil numbers as well as the Th2 cytokines IL-4, IL-5, eotaxin and RANTES (Yang et al., 2015). Another study tested the sEHI, GSK2256294A in a mouse model of cigarette smoke induced lung disease (Podolin et al., 2013). GSK2256294A attenuated cigarette smoke induced leukocyte infiltration and BAL chemokine levels by inhibiting inflammatory signaling and promoting resolution signaling. Interestingly, the antimicrobial agent triclocarban, used increasinglyin personal care products, is also a potent inhibitor of sEH and was recently tested in an LPS challenge mouse model (Liu et al., 2011). Again, the model showed that inhibition of sEH dramatically reduced LPS-induced inflammatory cytokine and chemokine production.

Although the currently available studies of interventions in animal models of air pollution related lung disease focus mainly on asthma and cigarette smoking, the commonality of disease processes suggest that these targets should also prove beneficial in other chronic lung diseases caused by exposure to diesel exhaust, wood smoke, industrial pollution, and other inhaled insults where continued chronic stimulation overwhelms the normal self-limiting nature of inflammation, leading to chronic inflammation and disease pathology.

7. Conclusion and future directions

Inflammation is normally a beneficial and self-limited process. There is now considerable evidence that chronic inflammation represents a failure to resolve inflammation, and this failure is linked to dysregulation of SPMs and the pro-resolution pathways. Chronic lung inflammation may be especially difficult to resolve, since exposures to urban air pollution, diesel and traffic exhaust, and secondhand smoke, are often difficult to avoid, resulting in repeated insults. In COPD patients, the disease can persist and even worsen after smoking cessation, because the inflammatory cascade is self-perpetuating, with lung inflammatory cells producing reactive oxygen species and other pro-inflammatory signals that cause tissue damage and recruit further inflammatory cells. Although corticosteroids can be useful in treating acute inflammation and disease flare-ups, chronic use carries significant risks and side effects and does not address the underlying imbalance.

While dietary supplementation with fish oils and other sources of omega-3 may have some general benefits, their benefits in specific human chronic inflammatory diseases are unclear, although some trials are still ongoing. Therapeutic use of SPMs shows promise in cell culture and animal models of exposure to various categories of inhalation insult. The resolution program, broadly viewed, is a target-rich environment; potential therapeutics include SPMs and SPM derivatives, other synthetic small molecule agonists of SPM receptors, inhibitors of SPM-degrading enzymes, and modifiers of the SPM synthesis pathways. If therapies based on small inhibitor RNAs move out of the laboratory and into the clinic, the resolution program presents a rich array of potential targets.

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Conflicts of interest

The authors declare no conflicts of interest pertaining to this work.

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