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Resolvins: Natural Agonists for Resolution of Pulmonary Inflammation

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Abstract

Inappropriate or excessive pulmonary inflammation can contribute to chronic lung diseases. In health, the resolution of inflammation is an active process that terminates inflammatory responses. The recent identification of endogenous lipid-derived mediators of resolution has provided a window to explore the pathobiology of inflammatory disease and structural templates for the design of novel pro-resolving therapeutics. Resolvins (resolution-phase interaction products) are a family of pro-resolving mediators that are enzymatically generated from essential omega-3 polyunsaturated fatty acids. Two molecular series of resolvins have been characterized, namely E- and D-series resolvins which possess distinct structural, biochemical and pharmacological properties. Acting as agonists at specific receptors (CMKLR1, BLT1, ALX/FPR2 and GPR32), resolvins can signal for potent counter-regulatory effects on leukocyte functions, including preventing uncontrolled neutrophil swarming, decreasing the generation of cytokines, chemokines and reactive oxygen species and promoting clearance of apoptotic neutrophils from inflamed tissues. Hence, resolvins provide mechanisms for cytoprotection of host tissues to the potentially detrimental effects of unresolved inflammation. This review highlights recent experimental findings in resolvins research, and the impact of these stereospecific molecules on the resolution of pulmonary inflammation and tissue catabasis.

1. Introduction

Acute inflammation is an essential host response to danger signals, including potential infection, noxious stimulus or tissue injury [1]. However, non-resolving inflammation is linked to many chronic inflammatory diseases, including asthma, rheumatoid arthritis, inflammatory bowel disease, and psoriasis (reviewed in [2]). In association with clinical symptoms in these chronic inflammatory diseases are elevated levels of pro-inflammatory mediators [3]. The overall magnitude and duration of inflammation depends on competing physiological processes, namely pro-phlogistic mechanisms that amplify inflammation and endogenous braking programs that control the resolution of inflammation (reviewed in [4]). In health, progression through the resolution phase of inflammation is primarily driven by the orderly phagocytic clearance of apoptotic granulocytes and debris by macrophages [5,6]. It is now established that resolution of inflammation is an active coordinated process that is

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spatiotemporally controlled by endogenously generated autacoids at sites of inflammation [4,7,8]. The enzymatic transformation of polyunsaturated fatty acids (PUFAs) during inflammation leads to the generation of specific endogenous mediators that act as potent agonists for resolution by exhibiting anti-inflammatory, pro-resolving, anti-fibrotic, anti-angiogenic and anti-infective actions (reviewed in [4]). The discovery that PUFAs are indispensable for health and dietary deficiencies can lead to clinical symptoms of diseases was first established in the late 1920s [9]. Such pioneering work suggested a specific relationship between the immunoregulatory role of PUFAs and the pathogenesis of major human diseases. As such, the identification of PUFA-derived mediators generated locally during the resolution of inflammation has led to a rapidly advancing understanding of the cellular and molecular mechanisms that are fundamental to resolution. Here, we review recent insights into the resolution of airway inflammation, and in particular, highlight anti-inflammatory and pro-resolving roles for resolvins in inflammation and pulmonary diseases.

2. Resolution of acute inflammation

Resolution is now appreciated to be an active process that terminates acute inflammation. At present, we know that efficient restoration of inflamed tissues to their basal state requires that inflammatory cells are effectively cleared and further neutrophil recruitment is abrogated. During this process, tissue neutrophils undergo apoptosis and are recognized and subsequently engulfed by phagocytic macrophages in a non-inflammatory manner [5,6]. Clearance of apoptotic neutrophils leads to the production of additional mediators that suppress the progression of inflammation and promote repair of damaged tissues [10–12]. Dysregulation of this process leads to unresolved inflammation, which underlies the pathology of several chronic inflammatory disease processes [4,13,14]. Hence, resolution of inflammation requires a cellular flexibility in the affected tissues in order to re-establish a homeostatic state after a limited period of inflammation. This sequence of events is also referred to as 'catabasis' - the reversion from a pathological state to one that is non-inflammatory in restoring tissue homeostasis [1,7].

2.1 Emerging cellular and molecular concepts of resolution

Inflammation resolution is a dynamic program that is partially dependent on the equilibrium of leukocyte ingress and egress at inflamed sites (reviewed in [15]). Several cellular and molecular mechanisms can limit the acute inflammatory response, including lipid mediator class switching [16]. During acute inflammation, early phase prostaglandin (PG) E₂ and PGD₂ can decrease neutrophil leukotriene (LT) generation and increase expression of 15-lipoxygenase (15-LOX) to switch LOX-derived AA metabolism to the biosynthesis of lipoxins [16], which are stop signals for neutrophil transmigration and activation, as well as go signals for macrophage clearance of apoptotic neutrophils. Combined, these actions actively promote resolution by clearing inflammatory cells from the previously inflamed tissue.

Distinct macrophage subsets, termed resolution-phase macrophages and fibroblastic macrophages, can play an active role in promoting the resolution of acute inflammation via phagocytic clearance of leukocytes [17,18]. Neutrophil clearance from mucosal tissues can also proceed by transmigration from the apical epithelial surface into the lumen via an epithelial CD55-mediated process [19] (reviewed in [20]). Mucosal epithelium can also express antimicrobial peptides and lipoxins can enhance host defense at mucosal surfaces by inducing epithelial bactericidal/permeability-increasing protein (BPI) [21]. Apoptotic inflammatory cells also serve a pro-resolving role by sequestering and scavenging extracellular chemokines via upregulation of cysteine-cysteine (CC) chemokine receptor 5 (CCR5) [22]. Pro-resolving mediators also display potent effects on tissue resident cells, including anti-angiogenic and anti-fibrotic actions [23,24]. These findings are relevant to

chronic inflammatory diseases of the lungs as both angiogenesis and fibrosis are recognized features of airway remodeling in asthmatic individuals and pulmonary fibrosis, respectively [25]. There is now increasing evidence that defined signal transduction pathways relay pro-resolution signals that impact on a diverse range of cellular events that are fundamental to resolution [14,26–30] (see Section 6). Targeting these pro-resolution pathways to control inflammation would constitute a novel therapeutic strategy for inflammatory disease.

2.2 Pro-resolution is distinct from anti-inflammation

As our understanding of the cellular and molecular mechanisms of inflammation has evolved, it has become apparent that anti-inflammation and pro-resolution are distinct physiological processes [31]. This concept is based on the initial identification of pro-resolving mediators generated at sites of inflammation that not only block granulocytic tissue entry and activation but also promote the clearance of inflammatory cells and debris from inflamed tissue (reviewed in [4]). An important functional distinction between endogenous pro-resolving mediators and pure anti-inflammatory mediators is the ability of pro-resolving mediators to accelerate the restitution of tissue homeostasis and clearance of inflammatory cells without concomitant immunosuppression. To this end, pro-resolving mediators signal for the recruitment of monocytes [32], uptake of apoptotic neutrophils by macrophages [33], increased chemokine scavenging capacity of apoptotic neutrophils (via CCR5 expression) [22], clearance of tissue neutrophils into the gastrointestinal mucosal lumen by CD55 expression [34] and enhanced mucosal host defense via expression of anti-microbial peptides by mucosal epithelial cells [21,35]. In a model and context-dependent manner, triggering of these pro-resolution pathways can stimulate the secretion of additional anti-inflammatory mediators, such as transforming growth factor (TGF)- β 1 and interleukin (IL)-10 that also dampen the magnitude of the inflammatory response [36,37].

Dysregulation of constitutive neutrophil apoptosis may prevent the resolution of pulmonary inflammation and is implicated in several neutrophilic lung diseases, such as acute respiratory distress syndrome (ARDS) [38], cystic fibrosis [39], chronic obstructive pulmonary disease (COPD) [40] and severe asthma [41]. The resolution of established inflammation can be expedited in model systems by promoting apoptosis of neutrophils [28]. Human neutrophils express functionally active cyclin-dependent kinases (CDK) and inhibiting their function with selective CDK inhibitors can directly induce caspase-dependent neutrophil apoptosis and override pro-survival signals mediated by GM-CSF [28]. In addition, engulfment of apoptotic neutrophils by phagocytes leads to release of pro-resolving mediators that can act in an autocrine manner to accelerate tissue catabasis [12]. Hence, neutrophil lifespan at sites of inflammation may influence the rate of resolution in inflammatory lung disease. Recently, quantitative cellular and tissue indices of resolution were introduced to objectively assess the impact of perturbations on resolution [17,36]. For instance, the resolution interval (R_i) for neutrophils during an inflammatory response is defined by the time interval between maximal neutrophil extravasation and the point that neutrophil numbers decline to one-half of the maximum [36]. By definition, factors that shorten this interval (R_i) accelerate resolution while measures that increase R_i delay resolution. It is highly likely that several dynamic cellular processes that determine neutrophil lifespan at sites of pulmonary inflammation may influence the R_i . These may include constitutive neutrophil apoptosis as well as alternative non-apoptotic death programmes, such as oncosis/necrosis [42,43], pyroptosis [43], cytolysis [44], NETosis [45] and autophagic-like neutrophil death pathways [46].

Currently available anti-inflammatory agents [*e.g.* glucocorticoids (GCs) and anti-tumor necrosis factor- α therapy] for the treatment of chronic diseases target biochemical and cellular processes by antagonising key pro-inflammatory mediator pathways. However, their chronic use is associated with potentially serious side effects, including immunosuppression

with increased susceptibility to a broad array of opportunistic bacterial, viral and fungal respiratory infections [47] and hospitalization for pneumonia results in a high COPD-related mortality rate amongst elderly patients [48]. Of relevance to pro-resolution, inhibitors of cyclooxygenases (COX) and lipoxygenases (LOX) can also interfere with the resolution process as these enzymes are also required for the endogenous formation of lipid-derived pro-resolving mediators. Hence, novel therapeutic agents that can promote anti-inflammation and endogenously exploit pro-resolution pathways to enhance host defense may have an advantageous therapeutic potential and would represent a novel concept in drug development (reviewed in [4], [49]).

3. PUFA-derived mediators regulate inflammation

PUFAs are essential for mammalian health. The ω -6 PUFA, arachidonic acid (AA; 20:4 n -6) is incorporated into cellular phospholipids, and upon cell activation, specific phospholipase A₂ enzymes hydrolyze the *sn*-2 fatty acyl bond of phospholipids to liberate AA. Once released, enzymatic metabolism of AA via COX or LOX give rise to bioactive mediators, such as prostaglandins, leukotrienes and lipoxins [50]. The ω -3 PUFAs, eicosapentaenoic acid (EPA; 20:5 n -3) and docosahexaenoic acid (DHA; 22:6 n -3) are enriched in neural and mucosal tissues [51,52] and in whole blood in healthy subjects - EPA accounts for ~0.5 to 2.8% of total fatty acids and DHA ~1.3 to 5.0% [53–57]. At sites of inflammation, these PUFAs are available for enzymatic transformation to distinct families of pro-resolving mediators that can regulate inflammation [7,8,58] and will be the focus of Section 3.

3.1 ω -6 arachidonic acid metabolism and generation of pro-resolving mediators - Lipoxins

Lipoxins (LXs) are the lead family of specialized endogenous mediators that were first to be recognized to exhibit both anti-inflammatory and pro-resolving actions (reviewed in [4]). They are synthesized from AA via sequential catalytic actions of LOXs to generate trihydroxy-tetraene-containing eicosanoids (reviewed in [59]). LXs are produced during cell-cell interactions and are structurally and functionally distinct from pro-inflammatory eicosanoids that are principally generated during the onset of inflammation. LXs are endogenously generated at sites of pulmonary inflammation and elicit a multitude of cell-type specific responses that are relevant to asthma resolution.

Resolution of asthma exacerbations is characterized by clearance of the lung inflammatory infiltrate, restoration of epithelial barrier function and amelioration of airway hyper-responsiveness [60]. LXs block granulocyte chemotaxis, trans-endothelial and trans-epithelial migration [61–66], suppress cytokine-mediated signalling in eosinophils [67], inhibit neutrophil azurophilic granule degranulation [68] and oxidative burst [26] and stimulate the non-phlogistic clearance of apoptotic neutrophils by macrophage phagocytosis [33]. In addition, LXs down-regulate the secretory potential of bronchial epithelial cells for pro-inflammatory cytokines [69]. Notably, many of these pro-resolving actions of LXA₄ are shared by its endogenous 15 R enantiomers, the aspirin-triggered 15-epimer-lipoxins (15-epi-LXs) [4,64,70,71]. Most recently, it has been shown that the endogenous synthesis of 15-epi-LXs can be regulated by statins during neutrophil-airway epithelial cell interactions *in vitro* and in bronchial mucosal inflammation *in vivo* [72].

In clinical asthma, several independent studies have reported that significantly lower levels of LXs are observed in plasma and the respiratory tract of severe asthmatics compared to patients with non-severe asthma [73–76]. In addition, circulating levels of LXA₄ correlate with lung function assessed by the measurement of forced expired volume in 1 sec (FEV₁, % predicted) [73]. Of note, alveolar macrophages can generate lipoxins and LXA₄ biosynthesis is also significantly decreased in alveolar macrophages from severe asthmatics compared to non-severe asthmatics and healthy subjects [77]. Further evidence for a

bronchoprotective role for LXs comes from a clinical study where LXA₄ administered to asthmatic subjects by the inhaled route effectively antagonised LTC₄-induced bronchoconstriction [78]. Moreover, evidence for a role of LXs in resolution of allergic asthma derives from the actions of LXA₄ and LXA₄ stable analogs that block both airway hyper-responsiveness and allergic airway inflammation in a murine model of allergic asthma [64,71,79]. Collectively, these findings indicate that pro-resolution mechanisms are compromised in severe asthma and that LXs, when present, can serve as endogenous agonists of anti-inflammation and pro-resolution to modulate asthma pathobiology.

3.2 ω -3 eicosapentaenoic and docosahexaenoic acid metabolism and generation of pro-resolving mediators – Resolvins

An exciting area in pro-resolving mediator research began with the identification of resolvins [8,58]. These endogenous autacoids are generated from the ω -3 PUFAs EPA and DHA to produce E-series (RvE) and D-series (RvD) resolvins, respectively, and together, the resolvins are a novel class of mediators that act as natural agonists at specific receptors to promote resolution [15,80–82]. Resolvins were first isolated from resolving exudates in murine dorsal air pouches after animals were treated with aspirin and EPA *in vivo*, and following co-incubation of human endothelial cells with neutrophils *in vitro* [8,58]. Resolvins are generated via interactions between aspirin acetylated COX-2 and LOX activities [58]. RvE1 biosynthetic intermediates can also be formed via a cytochrome P450-dependent process that is independent of aspirin [8,83]. There is now substantial evidence that resolvins elicit a multitude of endogenous anti-inflammatory, pro-resolving, anti-fibrotic, anti-angiogenic, anti-infective and anti-hyperalgesic actions (reviewed in Section 4). Primarily, these are achieved by signaling in a cell-type specific manner. Section 4 (*vide infra*) is devoted to reviewing the immunoregulatory actions of resolvins.

3.3 ω -3 docosahexaenoic acid metabolism and generation of pro-resolving mediators – Protectins and Maresins

Recently, additional classes of pro-resolution mediators derived from DHA have also been identified in resolving inflammatory exudates that display protective bioactivities, namely protectins and maresins (named for macrophage mediators in resolving inflammation) [84,85]. DHA-derived mediators are enzymatically generated via a LOX-initiated pathway [84–86]. At sites of inflammation, DHA is rapidly converted by LOX activity to 17S-hydroperoxy-DHA and via an epoxide containing intermediate to protectins, such as PD1 (10R,17S-dihydroxy-docosa-4Z,7Z,11E,13E,15Z,19Z-hexaenoic acid) [86] (for detailed reviews, see refs [4,15]). DHA can be delivered during the early stages of an acute inflammatory response in albumin-rich edematous fluid [87]. It is noteworthy that the cellular components of the airway mucosa are enriched with DHA [52] and both 17S-hydroxy-DHA and PD1 are generated in human airways [88]. Of interest, PD1 levels decrease during acute exacerbations of asthma and the bronchoprotective actions of PD1 have recently been demonstrated in a murine model of allergic asthma *in vivo* [88]. Using ovalbumin-sensitized mice, PD1 (2 – 200 ng) given by the intravenous route to sensitized mice prior to aeroallergen challenge markedly suppressed bronchial hyperresponsiveness, mucus secretion, pulmonary eosinophil accumulation and proinflammatory cytokine and lipid mediator release. PD1 also elicited a pro-resolving effect on established pulmonary inflammation when given after allergen challenge, leading to significantly expedited resolution of allergic airway inflammation [88]. The pro-resolving actions of maresins have recently been demonstrated during the resolution of murine peritonitis *in vivo* [85] and have not yet been examined in the context of pulmonary inflammation. Thus, these findings are consistent with the ability of these ω -3 PUFA-derived mediators to act as natural agonists for the resolution of pulmonary inflammation (Figure 1).

4. Resolvins: ω -3 PUFA-derived pro-resolving mediators

Two molecular series of resolvins have been identified and characterized, namely E- and D-series resolvins that are enzymatically derived from ω -3-derived-EPA and DHA, respectively. They were originally identified by physical methods during unbiased lipidomic analyses of resolving exudates [8,58]. It is now appreciated that resolvins elicit a range of cell-type specific responses that collectively block inflammation and promote resolution (reviewed in [4]). These catabatic actions *in vitro* and *in vivo* will be highlighted in this Section and are also summarized in Table 1.

4.1 Lipidomic analysis of resolving exudates to identify resolvins

The use of highly sensitive and specific analytical techniques, such as liquid chromatography ultraviolet/tandem mass spectrometry (LC-UV-MS-MS), has enabled lipidomic profiling of materials from inflammatory sites. The mouse dorsal air pouch is an experimental model of a dermal wound that provides a creative system for investigation of cellular and biochemical effectors of resolution during a self-limited acute inflammatory response. Inflammatory exudates were extracted and subjected to LC-UV-MS-MS-based lipidomic analyses by Serhan and colleagues, leading to the identification of E- and D-series resolvins (reviewed in [89]). Detailed matching studies for pro-resolving actions were performed to confirm the structure-activity relationships for each endogenous compound. For elucidation of stereochemical conformation of resolvins, retrograde analyses were performed using materials generated via biogenic and total organic synthesis [8,58,83,90]. Thus, application of these sensitive and specific analytical methodologies has uncovered resolvins and additional classes of pro-resolving mediators [91].

4.2 EPA-derived E-series resolvins

Two members of the E-series resolvins have been identified and are named resolvin E1 (RvE1) and resolvin E2 (RvE2). Both are endogenously generated from EPA and were initially isolated from *in vitro* and *in vivo* models of resolution [8,58]. Within the human vasculature, transcellular synthesis of RvE1 proceeds in the presence of aspirin with transformation of C20:5 to 18R-HEPE (18R-hydroxyeicosapentaenoic acid) by aspirin-acetylated COX-2 in endothelial cells. 18R-HEPE is subsequently converted by leukocyte 5-LOX to RvE1 via a 5(6) epoxide-containing biosynthetic intermediate [8,83] (Figure 2). In humans, RvE1 levels are increased in individuals taking aspirin and/or following dietary EPA supplementation [83]. The stereochemical assignment for RvE1 is 5S,12R,18R-trihydroxyeicosa-6Z,8E,10E,14Z,16-EPA [8,83]. Functionally, RvE1's actions are highly stereoselective both *in vivo* and *in vitro* [4]. RvE2 (5S,18(R/S)-dihydroxy-8Z,11Z,14Z,16E-eicosapentaenoic acid) is a structurally distinct member of the E-series resolvins yet displays similar bioactivities as RvE1 [92]. Administration of RvE1 and RvE2 in nanogram amounts exhibits additive cytoprotective effects [92].

4.3 DHA-derived D-series resolvins

The two major classes of D-series resolvins are positional isomers and have been named resolvins (RvD1 to RvD4) and aspirin-triggered (AT) resolvins (AT-RvD1 to AT-RvD4) [93]. The resolvins are enzymatically generated from DHA by 15-LOX-mediated conversion to 17S-hydroperoxyDHA (17S-HpDHA) and subsequent transformation by 5-LOX to RvD1 to RvD4 via epoxide containing intermediates (Figure 3). For the AT-resolvins, DHA is initially converted by aspirin acetylated COX-2 to 17R-HpDHA that is also a substrate for 5-LOX-mediated transformation to the epimeric form of the resolvins, namely AT-RvD1 to AT-RvD4 (Figure 4). Stereochemical conformation of RvD1, RvD2 and AT-RvD1 have been assigned as 7S,8R,17S,-trihydroxy-4Z,9E,11E,13Z,15E,19Z-DHA (RvD1), 7S,16R,17S-trihydroxy-docosa-4Z,8E,10Z,12E,14E,19Z-hexaenoic acid (RvD2) and 7S,8R,17R-

trihydroxy-4Z,9E,11E,13Z,15E,19Z-DHA (AT-RvD1) [90,94]. The determination of the complete stereochemistry of RvD3, RvD4, AT-RvD2, AT-RvD3 and AT-RvD4 is the subject of ongoing research.

4.4 Anti-inflammatory effects of resolvins on neutrophils

Neutrophils are critical to host defense, yet uncontrolled activation and/or delayed clearance of these granulocytes from inflamed sites can lead to unwanted bystander tissue damage and contribute to the pathogenesis of inflammatory disease, in particular in the lung [2,95,96]. Hence, limiting uncontrolled activation and accumulation of neutrophils at inflamed sites is an injury-limiting component of inflammatory resolution [4,5]. RvE1 inhibits neutrophil transmigration across endothelial and epithelial barriers to prevent tissue neutrophilia [8,35,80,97], down regulates expression of key neutrophil adhesion molecules (L-selectin, CD11b/CD18) [98], blocks neutrophil oxidative burst [99], stimulates non-phlogistic clearance of apoptotic neutrophils by inducing their engulfment by macrophages [80], and terminates chemokine signaling by upregulating decoy receptors (CCR5 expression) on apoptotic neutrophils during inflammatory resolution [22]. In mucosal tissues, RvE1 can enhance neutrophil clearance from the apical epithelial surface into mucosal lumen [35]. Additionally, RvE1 markedly suppresses pulmonary neutrophil accumulation in a murine model of acid-initiated acute lung injury (ALI) and aspiration pneumonia *in vivo* [100], adding to the already multifaceted roles of this resolvin in regulating neutrophilic inflammation (Table 1).

In addition to RvE1, RvD1 also blocks neutrophil inflammatory responses. At the single-cell level, RvD1 displays potent anti-inflammatory actions in a microfluidic chamber to inhibit IL-8-induced neutrophil chemotaxis [87]. Nanomolar concentrations of RvD1 block leukotriene B₄ (LTB₄)-stimulated actin polymerization and CD11b surface expression on human neutrophils [82]. RvD1 prevents transendothelial migration of human neutrophils and at nanogram doses *in vivo*, it potently suppresses neutrophil infiltration in murine peritonitis and ischemia reperfusion lung second organ injury [58,87,90]. RvD2 also effectively blocks tissue neutrophil accumulation. Zymosan-stimulated neutrophil infiltration in peritonitis is markedly decreased by RvD2 at doses as low as 10 pg [94]. RvD2 decreases excessive neutrophil recruitment to inflammatory loci and controls microbial sepsis after cecal ligation and puncture [94]. RvD2 can regulate neutrophil–endothelial interactions via direct modulation of adhesion molecule expression, namely decreased agonist-induced L-selectin shedding and CD18 expression on isolated human neutrophils [94]. Thus, resolvins can regulate neutrophil function to decrease extravascular granulocyte trafficking and aid the resolution response.

4.5 Pro-resolving actions of resolvins on macrophages

Macrophages can serve many pivotal functions in tissue catabasis. Efficient phagocytic removal of apoptotic granulocytes by macrophages is a key prerequisite for resolution of inflammation. Resolvins have a profound effect on the phagocytic activity of macrophages during the resolution process. Both RvD1 and RvE1 markedly increase ingestion of apoptotic neutrophils and thymocytes in isolated macrophages *in vitro* [80,101]. In addition, phagocytosis of zymosan A by human macrophages is greatly potentiated by RvE1 *via* phosphorylation-signalling pathways [102]. RvD1 also exhibits anti-inflammatory actions on a panel of macrophage-derived pro-inflammatory cytokines that are implicated in the pathogenesis of atherosclerosis [101]. Recently, it was shown that RvD1 regulates phagocytosis in a receptor-dependent manner in human macrophages [82].

In a murine model of acute kidney injury, resolvins exert cytoprotective actions as administration of D-series resolvins before the onset of ischemia effectively attenuates

morphological kidney injury and blocks lipopolysaccharide-induced activation of macrophages [103]. Resolution-phase macrophages (rM) have recently been identified and shown to possess unique pro-resolving phenotype in a murine model of peritonitis *in vivo* [104]. These rMs closely resemble an alternative phenotype of classically activated macrophages (M1) as they share many of same cellular markers (*i.e.* COX-2 and inducible nitric oxide synthase), yet differ from M1s by expression of the mannose receptor Ym-1, the enzyme arginase-1 and their ability to synthesize IL-10. Using an experimental model of peritonitis, RvE1 specifically modulated phenotypic switching of macrophages from M1 macrophages to rM macrophages [17] (Table 1). Thus, macrophages are an important target cell for the agonistic actions of resolvins, and regulation of phenotypic switching of macrophages from M1 to rM can alter the dynamics of inflammatory events and consequently expedite inflammation resolution.

4.6 Cytoprotective effects of resolvins on structural cells

The airway epithelium is an important physical barrier that regulates physiological processes, including leukocyte trafficking. In airway disease, interactions between damaged epithelium and inflammatory leukocytes contribute to the pathogenesis of common conditions, such as asthma [60,105,106]. Aberrant neutrophil-mucosal epithelial interactions are a key pathological process in such disease settings [72,106] and are likely to be re-programmed during resolution of pulmonary inflammation to prevent the accumulation of activated neutrophils. In mucosal inflammation, RvE1 can bind to its cognate receptor, chemokine-like receptor 1 (CMKLR1, see section 5.1) on epithelial cells to stimulate clearance of neutrophils into the gastrointestinal tract lumen in a CD55-dependent manner [35]. Resolvins also exert potent anti-angiogenesis activities during ocular neovascularisation as topical administration of RvE1 or RvD1 to inflamed murine corneas markedly down-regulates mRNA expression levels of TNF- α , IL-1 (alpha and beta) as well as vascular endothelial growth factors (A and C) in corneal epithelial and stroma-endothelial layers [107]. Comparable results have been obtained in a co-culture model of posterior ocular inflammation where pre-treatment with RvE1 significantly inhibited the release of pro-inflammatory chemokines in choroid-retinal endothelial cells alone and following their co-culture with neutrophils and monocytes *in vitro* [108].

It is well established that atherosclerosis is associated with vascular inflammation with endothelial cells expressing pro-inflammatory mediators and cell adhesion molecules that promote leukocyte adherence and extravasation [109]. Recent evidence supports a protective anti-atherogenic role for resolvins. RvD1 produces significant inhibition of human aortic endothelial cell release of neutrophil chemokines, including IL-8 and monocyte chemoattractant protein-1 (MCP-1) [101]. Both RvE1 and RvD1 potently block extravascular infiltration of neutrophils *in vivo* and modulate transmigration across monolayers of various types of endothelial cells *in vitro* [58,84,90]. RvD2 can trigger nitric oxide production by endothelial nitric oxide synthase (eNOS) in human umbilical vein endothelial cells (HUVEC) to modulate leukocyte trafficking [94]. Of additional interest in vascular medicine, receptors for RvE1 (CMKLR1 and BLT1) have been identified on human vascular smooth muscle cells (VSMCs) [110,111]. RvE1 blocks platelet-derived growth factor (PDGF)-stimulated chemotaxis of VSMCs isolated from human saphenous vein and decreases phosphorylation of the PDGF-R β [110].

The inflammation-resolving actions of resolvins are manifest in a cell- and tissue-specific manner (Table 1) (reviewed in [4]). For example, in human glioma cells [58], murine bone marrow-derived dendritic cells [112], murine primary osteoclast cultures [113] and human pancreatic islet cells, RvE1 displays potent cell-type specific actions [114]. Interestingly, retinal pigment epithelial cells and neural cells subjected to oxidative stress biosynthesize DHA-derived resolvins as a cytoprotective mechanism against oxidant injury [115,116].

Taken together, modulation of pro-inflammatory indices during both *in vitro* and *in vivo* models of human diseases are consistent with a bioprotective role for resolvins in regulating cellular responses in a cell-type specific manner to promote resolution of inflammation and injury.

5. Resolvin receptors

Details of pharmacological properties of resolvins are emerging and there are multiple receptors that transduce the potent pro-resolving actions of these compounds in a cell- and tissue-specific manner.

5.1 Receptors for E-series resolvins

RvE1 exerts its effects by acting via at least two distinct G protein-coupled receptors (GPCRs): CMKLR1 and the LTB₄ receptor 1 (BLT1). Originally characterized as a receptor for the chemotactic peptide, chemerin, CMKLR1 (aka ChemR23) is a G_{αi}-linked receptor expressed predominantly on monocytes/macrophages and plasmacytoid dendritic cells that mediate cell migration [117–119]. The binding of RvE1 to CMKLR1 was characterized using saturation binding analysis on CHO cells and it was established that human CMKLR1 exhibits high affinity for RvE1 ($K_d = 11.3 \pm 5.4$ nM) [83]. Phylogenetically, CMKLR1 shares homology with other chemoattractant receptors, including those for LXs (denoted ALX/FPR2, *vide infra*) and the neutrophil chemotaxins, C5a and C3a (C5aR and C3aR, respectively) [119]. RvE1 also mediates its effects through interactions with BLT1 receptors, as determined by radioligand binding analysis [81]. In humans, BLT1 receptors are expressed primarily by neutrophils, eosinophils, monocytes/macrophages, mast cells, dendritic cells, and effector T cells [120]. Binding studies have established that RvE1 binds to the human BLT1 with relatively lower affinity than CMKLR1 with a K_d value of 45 nM [81]. RvE1 effectively competes with LTB₄ for BLT1 binding to functionally antagonise LTB₄-mediated responses. In addition, RvE1 can serve as a potential agonist for BLT1 signaling. Hence, the pharmacology of these receptors exhibits agonist-specific adaptation where they transduce signals specific to each mediator. The RvE2 structure-activity relationship indicates that its actions are receptor-mediated, yet the molecular identity of the RvE2 receptor has not been established.

5.2 Receptors for D-series resolvins

Specific binding sites for RvD1 were recently identified on human leukocytes with subnanomolar affinity ($K_d = \sim 0.2$ nM) [82]. RvD1 interacts with phagocyte GPCR-32 (GPR32) as a potent agonist to signal for pro-resolving actions. In addition, RvD1 can directly activate ALX/FPR2 with high affinity ($EC_{50} \sim 1.2$ pM) and is as equipotent as LXA₄ ($EC_{50} \sim 1.1$ pM). The ALX/FPR2 receptor is upregulated during experimental airway inflammation and lung injury to serve as a mechanism for LX-mediated catabasis [64,69]. In addition to LXs, this receptor may also serve important roles for RvD1's pro-resolving actions in the airway and is the subject of ongoing research. Of interest, ALX/FPR2 expression is relatively decreased in eosinophils and neutrophils in severe asthma [76], raising the possibility that this condition represents a deficit in pro-resolving signaling. ALX/FPR2-deficient mice have been prepared and display ligand specific effects on leukocyte responses and experimental inflammation [121]. The other D-series resolvins demonstrate structure-activity relationships indicative of receptor-mediated signaling pathways, but these receptors have not yet been identified.

6. Intracellular signaling mechanisms for resolvins

6.1 Nuclear factor kappa B (NF- κ B)

The transcription factor NF- κ B is a critical regulator of innate immune responses. A wide range of pro-inflammatory cytokines, chemokines, adhesion molecules and enzymes are regulated by the NF- κ B pathway [122]. In addition, NF- κ B repression has been identified as a major inducer of granulocyte apoptosis [123,124], an integral part of the resolution of inflammation and is linked to the pathogenesis of chronic inflammatory lung diseases, including asthma and chronic obstructive pulmonary disease (COPD) [122,125]. Hence, interfering with NF- κ B signaling pathways may represent a feasible therapeutic strategy to manipulate apoptotic programs and consequently trigger the resolution of inflammation [14,126,127]. Several lines of evidence indicate that resolvins can modulate the NF- κ B signalling pathway. For instance, RvE1 can serve as an agonist at CMKLR1 to block TNF- α -induced activation of NF- κ B in a concentration-dependent manner [83]. RvE1 can also attenuate proinflammatory LTB₄-mediated BLT1 signaling by decreased activation of NF- κ B [81]. In primary osteoclast cultures derived from murine bone marrow, RvE1 acts via BLT1 receptors to inhibit the nuclear translocation of the p50 subunit of NF- κ B to modulate osteoclast differentiation and bone resorption [113]. In the distal colons of mice subjected to dextran sulfate sodium-induced colitis, RvE1 markedly inhibits phosphorylation of NF- κ B at serine residue 276 and decreases levels of proinflammatory mediators [128]. In a murine model of pneumonia, RvE1 inhibits the translocation and activation of NF- κ B (p65) in lung tissue homogenates and enhances bacterial clearance [100]. Collectively, these findings point to NF- κ B as an important downstream site of action for resolvins to modulate inflammatory responses and signal for resolution.

6.2 Kinases

Signal transduction pathways via the phosphatidylinositol 3-kinase (PI3-K) and the MAPK family member extracellular signal-regulated kinase (ERK) have a critical role in regulating intracellular signaling events, leading to pro-inflammatory reactions that are common in chronic inflammatory lung diseases, such as asthma and COPD [129]. PI3-Ks are a family of lipid kinases that synthesize phosphatidylinositol-3,4,5-trisphosphate (PtdIns(3,4,5)P₃), a lipid second messenger critical for the localisation and function of the downstream serine/threonine kinase, Akt (protein kinase B) (reviewed in [130]). Intracellular signalling via the PI3-K/Akt pathway plays an important role in regulating many cellular processes, especially granulocyte migration, activation and survival [131–133]. Similarly, the ERK 1/2 pathway represents a point of convergence for multiple signaling events thereby regulating important cellular functions and fate of human neutrophils [127,134,135]. RvE1-CMKLR1 interactions initiate the activation of PI3-K resulting in phosphorylation of Akt and ribosomal S6 protein via mTOR signalling [102]. RvE1 activation leads to ERK phosphorylation that is inhibited by the pan-selective PI3-K inhibitor wortmannin and a specific ERK 1/2 inhibitor PD98059 [102]. *In vitro*, RvE1 exerts direct protective actions on cardiomyocytes by regulating apoptotic programs in cells exposed to hypoxia or hypoxia/reoxygenation [136]. It does so by increasing phosphorylation of Akt, ERK1/2, and eNOS and attenuating the levels of key pro-apoptotic proteins, including caspase-3 and Bax. Of interest, RvE1 attenuates inflammatory pain via a glutamate ionotropic receptor mechanism in spinal dorsal horn neurons through inhibition of the ERK signaling pathway [137]. Hence, resolvins can regulate these pivotal signal transduction pathways that coordinate cellular responses ranging from anti-inflammation to anti-hyperalgesia.

7. Pro-resolving actions of resolvins in experimental models of lung disease –

E- and D-series resolvins display potent bioactivities *in vivo* in a wide range of experimental models of ocular, oral, dermal, gastrointestinal, renal and vascular inflammation, as well as in regulating angiogenesis, ischemia–reperfusion and hyperalgesia *in vivo* (Table 1). Recently, experimental models of lung disease have provided insights into cellular and molecular pro-resolving actions for resolvins in pulmonary inflammation and infection, which will be highlighted in this section.

7.1 Allergic asthma

Asthma is a chronic inflammatory disease of the conducting airways (reviewed in [60,138]). The pathogenesis of asthma is notable for excess generation of pro-inflammatory cytokines, chemokines, growth factors and eicosanoids and interactions with numerous inflammatory cell types [138]. As such, an anti-inflammatory therapeutic strategy designed to target a single pro-phlogistic mediator with selective neutralizing antibodies is unlikely to be successful, as there is a considerable degree of functional redundancy and cross-regulation amongst the intricate network of pro-inflammatory mediators and cell types within the airways. No current therapies for asthma are designed to selectively promote resolution of the pulmonary inflammation. Activation of pro-resolution signaling circuitry represents an alternate therapeutic approach for the control of asthmatic airway responses. Of interest, airway mucosal epithelial cells from individuals with asthma or cystic fibrosis have depleted stores of the ω -3-PUFA DHA compared with healthy control subjects [52]. Investigators have recently explored the potential beneficial actions of the ω -3-PUFA-derived resolvins in experimental models of airway mucosal inflammation. In a murine model of allergic asthma *in vivo*, RvE1 administered intravenously potently inhibits the development of allergic airway inflammation and when given during the resolution phase of inflammation, RvE1 accelerates the resolution of airway inflammation, mucus metaplasia and hyper-reactivity to methacholine. [79]. These RvE1-mediated bronchoprotective actions during resolution were related to the inhibition of Th17 effector lymphocytes and increased generation of interferon-gamma (IFN- γ) and LXA₄ [79]. RvE1 and an LXA₄ stable analog provided additive pro-resolving actions, yet there were important differences in their mechanism of action. For example, similar to RvE1, the LXA₄ analog decreased IL-17 in bronchoalveolar lavage fluids, but distinct from RvE1, the LXA₄ analog did not inhibit IL-23 production or increase IFN- γ levels. Together, these findings support the presence of independent pro-resolving signaling circuits for RvE1 and LXA₄ that converge on the regulation of IL-17 to hasten catabasis in this model of allergic asthma exacerbations. RvE1 is also bioactive when given intraperitoneally before and during the sensitization and aeroallergen challenge phases. RvE1 prevents the development of bronchial hyperresponsiveness, mucus eosinophil accumulation and T-helper type 2 (Th2) cytokine mediator release [*e.g.* IL-13] [139] (Table 1).

7.2 Acute lung injury and bacterial pneumonia

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are important conditions characterized by an over exuberant acute inflammatory response to noxious stimuli or infection (reviewed in [140]). Patients with ALI/ARDS suffer from a loss of barrier integrity in the airways and a robust neutrophil-enriched infiltration of the lung that fills the alveoli and compromises their capacity to oxygenate the tissues, leading to excess morbidity and mortality [140]. No medical therapies have proven effective in dampening acute inflammation in ALI/ARDS. To determine the endogenous mechanisms of resolution in the lung after injury, a self-limited experimental murine model was developed for acid-initiated ALI [141]. Simulating events associated with the aspiration of gastric acid,

hydrochloric acid is instilled into the airway to trigger ALI and animals are closely followed for cellular, metabolic and molecular responses. Peak inflammation and leakage permeability changes in the airway occur 12–24 h after acid instillation. When RvE1 is given intravenously just prior to acid, the amplitude of the neutrophil infiltration is dampened [100]. These actions are related to significant decrements in lung cytokines and chemokines, in particular, IL-1 β , IL-6 and MCP-1. In addition to injury from sterile noxious stimuli, infection of the lung is a common etiology for ALI/ARDS and can be associated with acid injury in the form of aspiration pneumonia [140]. To determine if the anti-neutrophil actions of RvE1 were also immunosuppressive, enteric bacteria (*Escherichia coli*) were instilled after acid injury in the presence or absence of RvE1. After acid-initiated ALI, bacterial clearance is impaired, as this injury disrupts host defense mechanisms in the airway [100]. Of interest, RvE1 markedly enhanced bacterial clearance in the lung, decreased the levels of pro-inflammatory cytokines and chemokines and improved survival after bacterial challenge [100] (Table 1). Together, these findings of RvE1-mediated decreases in neutrophil accumulation and increased bacterial clearance support the notion that the actions of resolvins are catabolic rather than immunosuppressive.

In addition to RvE1, RvD1 displays bronchoprotective effects as this compound markedly decreased ischemia–reperfusion injury of the lung [87]. Another source of ARDS/ALI and critical illness is sepsis and RvD2 displays multi-level pro-resolving actions in experimental sepsis induced by cecal ligation and puncture [94]. Elucidation of the pro-resolving mechanisms for these and other resolvins in ALI/ARDS and pulmonary inflammation is a focus of ongoing research.

8. Resolvins as potential novel pro-resolving pharmacotherapeutics in pulmonary inflammation

8.1 Resolvin stable analogs

PUFA-derived mediators are rapidly formed and rapidly inactivated by local metabolic pathways (reviewed in [4]). These compounds thus serve as autacoids with largely autocrine and paracrine effects. The pivotal metabolic pathways for resolvins have been uncovered, informing the development of stable analogs. In addition to natural resolvins, their mimetics may serve useful to enhance the compound's bioavailability, pharmacokinetics and pharmacodynamics. For example, 19-(*p*-fluorophenoxy)-RvE1 is an analog of RvE1 that resists metabolic inactivation and displays efficacious bioactivity as a pro-resolving mediator [142]. Thus, resolvins provide templates for structure-based drug design for potential use as pharmacotherapeutics in chronic inflammatory lung diseases, such as asthma [49].

8.2 Novel therapies for the treatment of asthma and chronic obstructive pulmonary disease (COPD)

Asthma and COPD are both obstructive lung diseases that have distinct pathological features in terms of their structural alterations [*i.e.*, remodeling] and inflammatory cell profiles [143]. However, as both asthma and COPD become more severe, the patterns of pulmonary inflammation become more similar mainly due to neutrophil-dominated inflammation [143,144]. Glucocorticoids (GCs) are still the mainstay therapy for controlling airway inflammation and are potent anti-inflammatory agents, in particular for eosinophils and select lymphocyte populations [145]. However, currently available therapies, including GCs, fail to halt the progression of the airway inflammation of COPD [129], or resolve the established neutrophil-enriched airway inflammation in either severe asthma or COPD. Hence, there is an important unmet medical need for additional therapies for COPD and

severe, steroid-refractory asthma that can enhance the resolution of these maladaptive airway inflammatory responses.

Given the pathological overlap of neutrophil-dominant inflammation in both COPD and severe asthma, one might predict that controlling inappropriate neutrophil accumulation and/or driving neutrophil apoptosis and their timely clearance would promote the resolution of the pulmonary inflammation. Of interest, both the pro-inflammatory mediator LTB₄ and the pro-resolving mediator RvE1 can interact with BLT1 receptors. LTB₄ promotes neutrophil chemotaxis and activation and has been implicated to play a pathological role in COPD with markedly increased levels in the airway secretions of patients with COPD [148]. RvE1 can antagonize LTB₄ activation of BLT1 receptors that are expressed on neutrophils and select populations of effector T lymphocytes. Inhibition of LTB₄-mediated activation of these inflammatory cells may provide a mechanism for RvE1 to block acute inflammation and, in combination with its CMKLR1-mediated actions on macrophages, to accelerate resolution of these chronic lung diseases.

9. Conclusions

The recent discovery of resolvins, endogenously generated from essential ω -3 PUFAs, has helped to redefine our understanding of events that terminate inflammation by uncovering their pro-resolving roles in driving inflamed tissues to a non-inflammatory state. There is now substantial evidence that these stereospecific molecules play a vital role in governing the resolution of inflammation. Resolvins are enzymatically generated during cell-cell interactions and serve as mediators of resolution circuits *in vivo*. Resolvins are agonists for catabasis that exert regulatory actions relevant to lung inflammation. Specifically, these endogenous autacoids have a profound effect on blunting the inflammatory response by inhibiting aberrant neutrophil trafficking and activation, stimulating phagocytosis of apoptotic cells and debris by macrophages and promoting anti-angiogenic, anti-infective and anti-fibrotic actions. These multifaceted pro-resolving actions of resolvins indicate the highly specialised handling of pathophysiological changes during established inflammation in order to expedite inflammatory resolution and restore homeostasis. The integration of resolvins into the wider array of anti-inflammatory and pro-resolving signals, including lipoxins, protectins and maresins is the subject of ongoing and future investigation.

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Abbreviations

AA	arachidonic acid
ALI	acid lung injury
ALX/FPR2	lipoxin A ₄ receptor/ Formyl peptide receptor 2
ARDS	acute respiratory distress syndrome
ATL	aspirin-triggered lipoxin
AT-RvD1	aspirin-triggered-resolvin D1 (7 <i>S</i> , 8 <i>R</i> , 17 <i>R</i> -trihydroxy-docosa-4 <i>Z</i> , 9 <i>E</i> , 11 <i>E</i> , 13 <i>Z</i> , 15 <i>E</i> , 19 <i>Z</i> -hexaenoic acid)

AT-RvD2	aspirin-triggered-resolvin D2 (7 <i>S</i> , 16 <i>R</i> , 17 <i>R</i> -trihydroxy-docosa-4 <i>Z</i> , 8 <i>E</i> , 10 <i>Z</i> ,12 <i>E</i> , 14 <i>E</i> , 19 <i>Z</i> -hexaenoic acid)
AT-RvD3	aspirin-triggered-resolvin D3 (4 <i>S</i> , 11 <i>R</i> , 17 <i>R</i> -trihydroxy-docosa-5, 7 <i>E</i> , 9 <i>E</i> , 13 <i>Z</i> ,15 <i>E</i> , 19 <i>Z</i> -hexaenoic acid)
AT-RvD4	aspirin-triggered-resolvin D4. (4 <i>S</i> , 5 <i>R</i> , 17 <i>R</i> -trihydroxy-docosa-6 <i>E</i> , 8 <i>E</i> , 10 <i>Z</i> , 13 <i>Z</i> , 15 <i>E</i> , 19 <i>Z</i> -hexaenoic acid)
BALF	bronchoalveolar lavage fluid
BLT1	LTB ₄ receptor
BPI	bactericidal/permeability-increasing protein
CDK	cyclin-dependent kinases
CHO	chinese hamster ovary
CMKLR1	chemokine receptor-like 1
COPD	chronic obstructive pulmonary disease
COX-2	cyclooxygenase-2
DHA	docosahexaenoic acid
eNOS	endothelial nitric oxide synthase
EPA	eicosapentaenoic acid
fMLP	<i>N</i> -formyl-methionyl-leucyl-phenylalanine
GCs	Glucocorticoids
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GPCR	G protein-coupled receptor
HUVEC	human umbilical vein endothelial cells
LC-UV-MS/MS	liquid chromatography-ultraviolet spectrometry-tandem mass spectrometry
LOX	lipoxygenase
LTB₄	leukotriene B ₄ (5 <i>S</i> , 12 <i>R</i> -dihydroxy-eicosa-6 <i>Z</i> , 8 <i>E</i> , 10 <i>E</i> , 14 <i>Z</i> -tetraenoic acid)
LXA₄	lipoxin A ₄ (5 <i>S</i> , 6 <i>R</i> , 15 <i>S</i> -trihydroxy-eicosa-7 <i>E</i> , 9 <i>E</i> , 11 <i>Z</i> , 13 <i>E</i> -tetraenoic acid)
M1	classically activated macrophages
mTOR	mammalian target of rapamycin
NF-κB	nuclear factor kappa B
ω-3	omega-3
ω-6	omega-6
PD1	protectin D1 (10 <i>R</i> , 17 <i>S</i> -dihydroxy-docosa-4 <i>Z</i> , 7 <i>Z</i> , 11 <i>E</i> , 13 <i>E</i> , 15 <i>Z</i> , 19 <i>Z</i> -hexaenoic acid)
PDGF	platelet-derived growth factor
PI3-K	phosphatidylinositol 3'-kinase

PUFA	polyunsaturated fatty acid
rM	resolution-phase macrophages
RvD1	resolvin D1 (7 <i>S</i> , 8 <i>R</i> , 17 <i>S</i> -trihydroxy-4 <i>Z</i> , 9 <i>E</i> , 11 <i>E</i> , 13 <i>Z</i> , 15 <i>E</i> , 19 <i>Z</i> -docosaehaenoic acid)
RvD2	resolvin D2 (7 <i>S</i> , 16 <i>R</i> , 17 <i>S</i> -trihydroxy-docosa-4 <i>Z</i> ,8 <i>E</i> , 10 <i>Z</i> , 12 <i>E</i> , 14 <i>E</i> , 19 <i>Z</i> -hexaenoicacid)
RvD3	resolvin resolvin D3 (4 <i>S</i> , 11, 17 <i>S</i> -trihydroxy-5 <i>E</i> , 7 <i>E</i> , 9 <i>E</i> , 13 <i>Z</i> , 15 <i>E</i> , 19 <i>Z</i> -docosaehaenoic acid)
RvD4	resolvin D4 (4 <i>S</i> , 5, 17 <i>S</i> -trihydroxy-6 <i>E</i> , 8 <i>E</i> , 10 <i>Z</i> , 13 <i>Z</i> , 15 <i>E</i> , 19 <i>Z</i> -docosaehaenoic acid)
RvE1	resolvin E1 (5 <i>S</i> ,12 <i>R</i> ,18 <i>R</i> -trihydroxy-6 <i>Z</i> ,8 <i>E</i> ,10 <i>E</i> ,14 <i>Z</i> ,16 <i>E</i> -eicosapentaenoic acid)
RvE2	resolvin E2 (5 <i>S</i> ,18 <i>R</i> -dihydroxy-8 <i>Z</i> ,11 <i>Z</i> ,14 <i>Z</i> ,16 <i>E</i> -eicosapentaenoic acid)
TGF-β	transforming growth factor -beta
TNF-α	tumor necrosis factor-alpha
VSMCs	vascular smooth muscle cells

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Figure 1.

Figure 2.

Figure 3.

Figure 4.

Table 1

Pro-resolving effects evoked by resolvins *in vivo* in experimental disease models.

Agonist of resolution	Experimental disease model	Species	Pro-resolving/anti-inflammatory actions	Cell Target/Receptor	Ref.
EPA-derived E series					
Resolvin E1 (RvE1)	Acute lung injury	Mouse	Attenuates acid-initiated ALI, blocks neutrophil trafficking and pro-inflammatory mediator release.	Airway epithelium leukocytes	[100]
	Allergic asthma	Mouse	Expedites resolution of lung inflammation, inhibits bronchial hyperresponsiveness, mucus secretion, eosinophil recruitment. Up-regulates IFN- γ and LXA ₄ release. Prevents bronchial hyperresponsiveness, mucus secretion, eosinophil accumulation and Th2 cytokine mediator release.	Airway epithelium, eosinophil	[79] [139]
	Angiogenesis	Mouse	Decreases neutrophil recruitment and suppresses pro-inflammatory gene expression.	Corneal epithelium, neutrophil, macrophage / ChemR23	[107]
	Colitis	Mouse	Decreases neutrophil recruitment and down-regulates pro-inflammatory gene expression.	Gut epithelium, neutrophil, macrophage / ChemR23	[97,128]
	Diabetes	Mouse	Upregulates adipokines and induces insulin regulatory genes glucose transport (GLUT)-4 and insulin receptor substrate (IRS)-1. Protects liver from obesity-induced insulin resistance and hepatic steatosis.		[149]
	Dorsal air pouch	Mouse	Cessation of neutrophil trafficking, attenuates transepithelial/transendothelial migration.	Neutrophil / BLT1	[8,58]
	Inflammatory Pain	Mouse	Alleviates inflammatory pain induced by tissue injury, nerve injury and capsaicin treatment. Cessation of neutrophil trafficking, reduces paw edema, blocks pro-inflammatory mediator release.	Dorsal root ganglion/spinal cord neurons / ChemR23	[150]
	Ischaemia-reperfusion injury in the heart	Rat	Cardio-protective actions against ischaemia-reperfusion injury and limits infarct size on myocardium.	Cardiomyocytes	[136]

Agonist of resolution	Experimental disease model	Species	Pro-resolving/anti-inflammatory actions	Cell Target/ Receptor	Ref.
	Periodontitis	Rabbit Mouse	Cessation of neutrophil trafficking, inhibits connective tissue and bone loss, modulates osteoclast differentiation and bone resorption	Neutrophil, osteoclasts / BLT1	[113,151, 152]
	Peritonitis	Mouse	Cessation of neutrophil trafficking, regulates chemokine/cytokine production. Stimulates phagocytic clearance of apoptotic neutrophils. Initiates phenotypic switching of macrophages	Neutrophil, dendritic cell, macrophage / BLT1 ChemR23	[17,22,36, 80,83,87]
	Pneumonia	Mouse	Promotes clearance of <i>E. coli</i> pneumonia, blocks neutrophil trafficking and pro-inflammatory mediator release, reduces mortality.	Airway epithelium	[100]
	Retinopathy	Mouse	Diminishes vaso-obliteration and neovascularisation.	Choroid-retinal endothelial cells	[153]
Resolvin E2 (RvE2)	Peritonitis	Mouse	Cessation of neutrophil trafficking.	Neutrophil	[92]
DHA-derived D-series					
Resolvin D1 (RvD1)	Angiogenesis	Mouse	Decreases neutrophil recruitment and counter-regulates pro-inflammatory gene expression.	Corneal epithelium, neutrophil, macrophage	[107]
	Dorsal air pouch	Mouse	Cessation of neutrophil trafficking, attenuates transepithelial/transendothelial migration.	Neutrophil	[58,84]
	Inflammatory Pain	Mouse	Lowers amplitude of carrageenan and complete Freund's adjuvant-evoked heat hyperalgesia. Reduces incision-induced post-operative pain.	Dorsal root ganglion/spinal cord neurons / ChemR23	[150]
	Ischaemia-reperfusion injury in the lung and kidney	Mouse	Limits neutrophil trafficking to protect against ischaemia-reperfusion damage. Exerts anti-fibrotic actions to regulate macrophage function.	Neutrophil, macrophage	[87,103]
	Peritonitis	Mouse	Cessation of neutrophil trafficking, regulates chemokine/cytokine production, stimulates phagocytic clearance of apoptotic neutrophils. Protects against oxidative stress-initiated	Neutrophil, dendritic cell, macrophage	[84,87,90, 94]

Agonist of resolution	Experimental disease model	Species	Pro-resolving/anti-inflammatory actions	Cell Target/ Receptor	Ref.
inflammation.					
	Retinopathy	Mouse	Diminishes vaso-obliteration and neovascularisation.	Choroid-retinal endothelial cells	[153]
Resolvin D2 (RvD2)	Sepsis	Mouse	Cessation of neutrophil trafficking by inhibiting neutrophil-endothelial interaction, blocks cytokine production. Stimulates phagocytic clearance of apoptotic neutrophils.	Neutrophil, macrophage, endothelial cell	[94]