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Specialized pro-resolving mediators: endogenous regulators of infection and inflammation

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Abstract

Specialized pro-resolving mediators (SPMs) are enzymatically derived from essential fatty acids and have important roles in orchestrating the resolution of tissue inflammation — that is, catabasis. Host responses to tissue infection elicit acute inflammation in an attempt to control invading pathogens. SPMs are lipid mediators that are part of a larger family of pro-resolving molecules, which includes proteins and gases, that together restrain inflammation and resolve the infection. These immunoresolvents are distinct from immunosuppressive molecules as they not only dampen inflammation but also promote host defence. Here, we focus primarily on SPMs and their roles in lung infection and inflammation to illustrate the potent actions these mediators play in restoring tissue homeostasis after an infection.

Acute inflammation is a vital response to infection that is initiated within seconds of pathogen detection[1]. Granulocytes are rapidly recruited to sites of infection[2], where they become activated and augment the resident capacity of infected tissue to kill and ultimately clear the pathogen[3]. These early events in the host response to infection are essential for survival and are coordinated by several families of pro-inflammatory mediators, including lipid mediators (such as prostaglandins and leukotrienes), cytokines and chemokines. These pro-inflammatory mediators have overlapping and distinct functions and ultimately induce an increase in vascular permeability and orchestrate leukocyte recruitment. This leads to the cardinal signs of tissue inflammation — namely *calor*, *rubor*, *tumor*, *dolor* and potentially *functio laesa* (FIG. 1).

Recently, a new array of molecules that function in the resolution of inflammation were elucidated and named specialized pro-resolving mediators (SPMs)[4,5]. Many of these SPMs are produced during the acute inflammatory response[6], and their structure, biosynthesis and organic synthesis have been recently reviewed (see REF. 5). Typically, acute inflammatory responses to pathogens are self-limiting, and there is a growing appreciation that SPMs have pivotal anti-inflammatory and anti-infective roles in tissue catabasis[4]. For effective

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resolution of inflammation to occur in tissues, cessation of granulocyte recruitment is required in conjunction with the recruitment and differentiation of macrophages, which help clear inflammatory cells and tissue debris to restore tissue homeostasis[7]. Granulocytes in the tissue undergo apoptosis during the resolution of inflammation to prevent bystander tissue injury occurring from the release of potentially toxic cellular contents[8]. Removal of apoptotic neutrophils prompts a switch from a pro- to an anti-inflammatory macrophage phenotype, which is a prerequisite for macrophage efferocytosis and egress via the lymphatic vessels[9]. Efferocytosis also leads to further production of additional SPMs that signal for restoration of vascular integrity, regeneration and/or repair of injured tissues, remission of fever by inhibition of pro-inflammatory lipid mediators and cytokines, and relief of inflammatory pain[10]. Together, the SPMs and these cellular events in resolution can be summarized as the newly recognized five cardinal signs of resolution (FIG. 1).

In this Review, we address the functions of SPMs in infectious immunity and chronic inflammatory diseases, with a focus on how SPMs affect lung physiology and pathology in these diseases. Recent discoveries[11–15] regarding anti-inflammatory, anti-infective and pro-resolving roles for SPMs point to their potential translational applications in harnessing endogenous resolution responses for novel host-directed therapeutic strategies in sterile and infectious inflammation. Additional roles in these homeostatic processes for non-lipid mediators of resolution will not be covered in detail here but have been recently reviewed (see REFS 16–18). Cellular and molecular mechanisms for catabasis have now been determined in multiple organ systems and diseases. Here, we will primarily focus on lung infection and inflammation. The resolution responses that occur in non- pulmonary sites of infection and inflammation have recently been reviewed (see REFS 7,19–21). Finally, we consider how new therapeutic strategies that incorporate immunoresolvents may have the potential to synergize with antibiotics and to mitigate the growing problem of antibiotic resistance.

SPM production

In response to pathogen invasion or tissue injury, poly-unsaturated fatty acids are released locally from membrane phospholipids or delivered to sites of inflammation by tissue oedema for subsequent conversion to specialized mediators by cells in the exudates[22]. Within minutes, the generation of eicosanoids (that is, prostaglandins and cysteinyl leukotrienes) from arachidonic acid (C20:4*n*-6) metabolism helps to direct peripheral blood neutrophils to infected sites. Prostaglandin E_2 (PGE_2) and PGI_2 regulate blood flow, whereas leukotriene C_4 (LTC_4) and LTD_4 regulate vascular permeability[1,23]. Furthermore, neutrophils transmigrate towards chemotactic gradients of LTB_4 (REF. 24). With selected cytokines, chemokines and complement components (namely C5a and C3b), these eicosanoids induce neutrophil entry into the tissue to engulf and kill invading pathogens[3,25]. Early in the acute inflammatory response, the origins are laid for biosynthesis of resolution-phase mediators through lipid mediator class-switching, in which arachidonic acid metabolism switches from the production of leukotrienes to the production of lipoxins — the lead family of pro-resolving mediators[26]. Disruption of lipoxin formation or lipoxin receptor availability delays the resolution response[27–30].

As a class, the SPMs are enzymatically derived from essential fatty acids, including arachidonic acid, eicosapentaenoic acid (EPA; C20:5*n*-3) and docosahexaenoic acid (DHA; C22:6*n*-3) in a lipoxygenase (LOX)-dependent manner (FIG. 2). SPMs are stereoselective, and complete stereochemical assignment for the majority of the SPMs has been established (reviewed in REF. 31). Lipoxins are formed by transcellular biosynthesis via multiple distinct pathways. One pathway involves leukocyte- derived 5-LOX and platelet-derived 12-LOX in the vasculature[32]. A second pathway involves the conversion of arachidonic acid by epithelial cell-, eosinophil-or monocyte-derived 15-LOX and leukocyte- derived 5-LOX[33,34]. Although aspirin inhibits prostaglandin production, aspirin-mediated acetylation of cyclooxygenase 2 (COX2; also known as PTGS2) leads to the conversion of arachidonic acid to 15(*R*)-hydroxyeicosatetraenoic acid (15(*R*)-HETE), which can serve as a substrate for 5-LOX-mediated conversion to 15-epilipoxins (also known as aspirin-triggered (AT) lipoxins)[35]. Of note, in the absence of aspirin, 15(*R*)-HETE can also be produced by cytochrome P450 enzymes to act as a substrate for 15-epi-lipoxin transcellular biosynthesis[36,37].

In addition to lipoxins, resolving exudates also contain pro-resolving mediators derived from omega-3 fatty acids. These include resolvins, protectins and maresins (reviewed in REF. 38) (FIG. 2). E-series and D-series resolvins are enzymatically derived from EPA and DHA, respectively. Similarly to 15-epi-lipoxins, resolvins are generated through interactions between aspirin-acetylated COX2 and LOX activities[39]. For example, in the vasculature, resolvin E1 (RvE1) transcellular synthesis in the presence of aspirin is notable for transformation of EPA to 18(*R*)-hydroxyEPA (18(*R*)-HEPE) by aspirin-acetylated COX2 in endothelial cells and 18(*R*)-HEPE conversion to RvE1 by leukocyte 5-LOX[40,41]. There are two major series of resolvins that are derived from DHA, namely D-series resolvins (RvD1–RvD6) and their positional AT isomers (AT-RvD1–RvD6)[42]. The D-series resolvins are enzymatically generated by 15-LOX-mediated conversion of DHA to 17(*S*)-hydroperoxyDHA (17(*S*)-HpDHA) and subsequent transformation by 5-LOX. For the AT-resolvins, DHA is initially converted by aspirin-acetylated COX2 to 17(*R*)-HpDHA that can also serve as a substrate for 5-LOX-mediated transformation to epimeric resolvins. Additional families of pro-resolution mediators derived from DHA have also been identified in resolving inflammatory exudates that display protective bioactivities, namely protectins and maresins[43,44]. At sites of inflammation, 15-LOX-derived 17(*S*)-HpDHA can be converted to protectin D1 (REF. 45), and 12-LOX-derived 14(*S*)-HpDHA can be converted to maresin 1 (MaR1) (for a detailed review, see REF. 31). The respiratory tract mucosa in health is enriched with DHA[46], and both 17(*S*)-hydroxy-DHA and protectin D1 are generated in human airways[47].

These SPMs exert their bioactions as molecular signals via agonist properties at cognate receptors (FIG. 2). The lipoxin A_4 (LXA_4) receptor ALX (also known as FPR2) is a G protein-coupled receptor that binds LXA_4 and 15-epi-LXA_4 with high affinity. High-affinity receptors have also been identified for RvE1 (namely, chemokine-like receptor 1 (CMKLR1; also known as CHEMR23))[41], for RvD1 (namely, the probable G protein- coupled receptor GPR32) and for RvD2 (namely, the *N*-arachidonyl glycine receptor GPR18)[48,49]. Of interest, RvD1 can also activate ALX with high affinity and is equipotent to LXA_4 in binding and activating this receptor[49]. In addition to RvD1, AT-RvD1 and RvD3 bind to

GPR32 with high affinity[49–51]. These SPMs display potent receptor-mediated cell-specific actions (TABLE 1). Pharmacological structure activity relationships support receptor-dependent signalling mechanisms for the remaining SPMs; however, the molecular identity of their cognate receptors is still to be determined.

As is the case with lipoxins, defects in these SPM pathways can undermine resolution and contribute to chronic inflammation[27,30,52–55]. Failure of the resolution response may occur as a result of defects in receptor expression, enzyme synthesis, intracellular signalling or nutritional deficiencies in essential polyunsaturated fatty acids. Functional roles bring these structurally distinct families of lipoxins, resolvins, protectins and maresins together as SPMs — a genus of endogenous molecules that pharmacologically act as immunoresolvents[4].

Pro-resolving mediators are active in the picogram to nanogram dose range, whereby they are able to control inflammation, limit tissue damage, shorten resolution intervals, promote healing and alleviate pain in experimental models of inflammation and resolution. These fatty acid-derived mediators are part of a larger resolution programme that includes annexin A1 protein[16], several cytokines (for example, transforming growth factor-β (TGFβ) and interleukin-10 (IL-10))[11], microRNAs[51] and carbon monoxide[56]. Inhibitors of cyclin-dependent kinases can also pharmacologically promote resolution[57].

Cellular targets of SPMs

Counter-regulation of the acute inflammatory response evolved to neutralize and eliminate pathogens and enable repair of inflamed or injured tissues. The main cellular events of resolution are the cessation of neutrophil influx and activation, in conjunction with macrophage recruitment, efferocytosis and phagocytosis of microorganisms and debris[6,58]. As a class of mediators, SPMs are partly defined by their overlapping function to limit neutrophil tissue accumulation, counter-regulate pro- inflammatory cytokines and encourage macrophage phagocytosis (FIG. 3). During efferocytosis, phagocytes generate SPMs that serve as autacoids to inhibit neutrophil activation, increase apoptotic cell expression of CC-chemokine receptor 5 (CCR5) for chemokine clearance and promote bacterial killing and efferocytosis by macrophages (TABLE 1). In addition to phagocytes, lymphoid cells have vital roles in host defence, express SPM receptors and can serve as cellular effectors for SPMs. In this section, we highlight selected cell types with important functions in resolution and host defence that respond to SPMs.

Neutrophils

For tissue resolution of inflammation, it is essential to prevent further neutrophil entry, inhibit tissue neutrophil activation and promote the clearance of apoptotic neutrophils. All of these cellular actions are mediated by SPMs. Of particular note, SPMs initiate leukocyte shape changes that limit neutrophil migration *in vitro*[22], diapedesis *in vivo* and reduce tissue inflammation and damage[29,47,59–61]. For neutrophils, SPMs have potent anti-inflammatory actions, including decreased cell activation, adhesion and reactive oxygen species generation and increased microbial clearance (reviewed in REF. 4).

Macrophages

Both tissue-resident and recruited inflammatory macrophages serve pivotal roles in responses to infection and inflammation. SPMs augment macrophage functions to clear microorganisms, tissue debris and apoptotic cells (reviewed in REF. 6). In contrast to neutrophils, SPMs lead to macrophage shape changes that prepare the cells for phagocytosis of microorganisms, apoptotic cells and debris[9,12,62,63]. Key macrophage actions for SPMs include increased phagocytosis and IL-10 production and decreased pro-inflammatory cytokine production[9,64,65].

Natural killer cells

Natural killer (NK) cells can help promote the resolution of an inflammatory response by inducing neutrophil[66] and eosinophil apoptosis[67], which is a non-inflammatory mechanism for cell removal from tissues and has a crucial role in successful resolution of the inflammatory response[8]. Apoptotic granulocytes can subsequently be removed by tissue macrophage efferocytosis before tissues are exposed to their potentially toxic contents. By accelerating granulocyte apoptosis, NK cells can limit pathogen-mediated inflammatory responses. NK cells express ALX[67], and LXA_4 increases NK cell-mediated apoptosis of eosinophils and neutrophils[67]. NK cells also express CMKLR1, which is the receptor for RvE1 (REF. 67), and NK cell depletion markedly impairs the protective actions of RvE1 *in vivo*[68].

Innate lymphoid cells

Group 2 innate lymphoid cells (ILC2s) are members of the family of innate-like leukocytes. ILC2s do not express T cell or B cell antigen receptors, or markers of other leukocyte lineages, but they serve important roles for host defence against helminth infections[69]. In response to epithelial-derived cytokines, such as IL-25, IL-33, thymic stromal lymphopoietin and mast cell-derived prostanoids (that is, PGD_2), ILC2s generate type 2 cytokines — IL-5 and IL-13 — in an antigen-independent manner[67]. Similarly to NK cells, ILC2s express receptors for pro-resolving mediators, including LXA_4 and RvE1 (REF. 67). LXA_4 and MaR1 can potently inhibit ILC2 release of pro-inflammatory cytokines[67,70]. MaR1 also promotes amphiregulin release by ILC2s[70], a protective response for restoring lung mucosal homeostasis after influenza infection[71].

Lymphocytes

Adaptive immune cells also have important roles in the active resolution of inflammation. CCR5 expression on apoptotic, activated T cells acts to sequester pro-inflammatory cytokines and terminate inflammation; a mechanism that is augmented by SPMs[72]. RvE1 decreases the production of pro-inflammatory cytokines, such as IL-23 and IL-17, to dampen the adaptive immune response, particularly T helper 17 (T_H17) cell responses[73]. Regulatory T cells are pivotal to controlling effector T cell proliferation and activation. Of note, MaR1 was recently identified as a potent inducer for the formation of regulatory T cells *in vivo* and *in vitro* in combination with TGFβ[70]. Only limited information is available on SPM actions on B cells, but RvD1 was recently shown to augment B cell antibody production and increase the number of antibody-producing B cells in a mouse influenza

vaccination model[74]. These emerging data on the regulation of adaptive immunity by SPMs extend their range of actions and suggest a pivotal role for these imunoresolvents in the transition from innate to adaptive inflammation.

Mucosal epithelial cells

In mucosal host defence, transmigrating neutrophils initiate a respiratory burst and degranulation response to invading pathogens; however, excessive neutrophil activation can cause 'bystander' tissue damage and contribute to pathobiology of mucosal inflammatory disease[75]. During resolution, the activated neutrophils are cleared apically from the intestinal lumin by decay accelerating factor (also known as CD55), which is an anti-adhesive molecule[76]. SPMs potently inhibit neutrophil *trans*-epithelial migration and the production of pro-inflammatory cytokines by epithelial cells[77]. In addition, SPMs promote decay accelerating factor expression in mucosal epithelia as well as expression of the anti-infective peptide bactericidal permeability-increasing protein and the lipopolysaccharide (LPS) detoxification enzyme alkaline phosphatase[78,79].

SPMs in infection

Although the role of SPMs has only recently been uncovered in tissue homeostasis, there is already a push to understand the functions of SPMs in infections. Studies on the role of SPMs in the modulation of host responses to various infectious diseases have highlighted a new therapeutic opportunity for targeting the host in infectious inflammation to complement antibiotic therapy. Some recent examples are provided in TABLE 2 and the following sections, in which we consider the roles of SPMs in bacterial, viral and fungal diseases.

SPMs in bacterial infection

Pneumonia

Although pneumonia typically initiates a self-limiting acute inflammatory response, in some individuals the inflammation is so severe that it leads to life-threatening hypoxaemia and respiratory failure — namely, the acute respiratory distress syndrome (ARDS) — which is discussed in greater detail in the next section. In *Escherichia coli*-induced pneumonia, the SPM LXA_4 promotes neutrophil apoptosis by inducing the phosphorylation of BCL-2-associated death promoter (BAD) and reducing the expression of the anti-apoptotic protein myeloid cell leukaemia sequence 1 (MCL1)[80], whereas RvE1 promotes neutrophil apoptosis through activation of caspases[81]. In both cases, promotion of neutrophil death leads to a reduction in the severity of acute lung inflammation[81,82]. These findings highlight a direct interaction between the SPMs and apoptotic pathways in immune cells. In addition, RvE1 enhances bacterial clearance and reduces local production of pro-inflammatory cytokines in *E. coli* aspiration pneumonia, which results in enhanced survival of mice[13].

Periodontitis

Bacterial periodontitis is a well- established experimental model that has been used to elucidate the role of SPMs in controlling localized bacterial infection, its associated tissue damage and systemic effects. Periodontitis is generally caused by a polymicrobial insult,

resulting in the generation of biofilms, overgrowth of resident Gram-negative bacteria in the oral cavity and mucosal inflammation. The disease process is thought to be mediated by an overly robust immune response to the bacteria, including to *Porphyromonas gingivalis* in chronic infection and *Actinobacillus* spp. in the localized aggressive form of the disease. Periodontitis also carries a more generalized implication to human health, as localized periodontitis elicits a systemic response, increasing systemic inflammation and risk for accelerated atherosclerosis[82,83].

In localized *P. gingivalis* infection models, introduction of stable analogues of lipoxins and AT-lipoxins results in a reduction of neutrophil recruitment to the site of infection[84]. In a rabbit model of the same infection, rabbits that either transgenically overexpress 15-LOX, the enzyme responsible for production of lipoxins and protectins, or are treated with a topical formulation of LXA_4 had a reduction in leukocyte infiltration in inflammation at the site of injury and a reduction in bone loss[85], highlighting a suppressive role for the lipoxins in the control of localized inflammation in this chronic infection. Furthermore, the systemic response to infection is attenuated, resulting in a decrease in neutrophil–platelet interactions[86] and limiting generalized systemic inflammation, as indicated by a reduction in biomarkers such as C-reactive protein[61].

Resolvins also have a role in promoting protection against bacterial periodontitis. In localized aggressive periodontitis (LAP), RvE1 suppresses neutrophil super-oxide generation[87], neutrophil infiltration[88] and the production of pro-inflammatory cytokines[88], and enhances macrophage activity[89]. At least some of its actions are mediated through its interaction with CMKLR1, which is highly expressed on macrophages and dendritic cells (DCs)[41]. In models of LAP, treatment of animals with topical RvE1 results in a decrease in localized and systemic inflammation and allows the host to regenerate lost tissue and bone mass[61]. The ability of RvE1 to reestablish homeostasis at the local tissue level proceeds in part through its ability to restore phagocyte activity of macrophages, which is impaired in LAP[90]. Lipoxin analogues or AT-lipoxins have no significant effect on neutrophil activity in LAP, which is in contrast to chronic periodontitis, in which LXA_4 has a regulatory role, highlighting a context-specific mechanism for the pro-resolving mediators.

Lyme disease

In a similar manner to periodontitis, a pattern of localized and systemic control of inflammation is seen in mouse models of Lyme disease. In 5-LOX-deficient mice, which have a defect in SPM production, the development of arthritis in animals infected with *Borrelia burgdorferi* is similar to that in wild-type animals; however, the absence of lipoxins and resolvins impairs the host ability to resolve arthritis, resulting in chronic disease[91] and a lack of control of the chronic systemic inflammatory response long after the triggering infectious agent has been cleared.

Tuberculosis

The protective roles for SPMs in acute infections, such as pneumonia, are also integral to the host immune response to *Mycobacterium tuberculosis*. In this host response, there is a delicate balance between pro-inflammatory mediators, such as PGE_2 and LTB_4, and pro-

resolving mediators, such as LXA_4, that can dictate the intensity of the pathogen-mediated inflammation as well as microbial clearance. In a mouse model of *M. tuberculosis* infection, there is a rise in the levels of both the pro-inflammatory LTB_4 and the pro-resolving LXA_4 after infection, with LXA_4 high levels persisting throughout the chronic infection[92]. In animals deficient in 5-LOX (a deficiency that leads to defective leukotriene and lipoxin production), *M. tuberculosis* infection is associated with enhanced survival[92]. Host lipoxin generation is related to *M. tuberculosis* strain virulence, suggesting a vital role for SPMs in modulating the host inflammatory responses to *M. tuberculosis*. Excessive production of either LTB_4 or LXA_4 can result in aberrant host responses to *M. tuberculosis* infection that, intri guingly, converge on dysregulated expression of TNF[15]. This accentuates the importance of both pro-inflammatory and pro-resolving responses for host defence and regulation of pathogen-mediated inflammation. Crucial roles for arachidonic acid metabolism in immune responses may be linked to the different infectious rates observed with human variants in the *ALOX5* (encoding 5-LOX) locus[93] and the *LTA4H* (which encodes LTA_4 hydrolase, an enzyme involved in the final step of LTB_4 production) locus[94], which both appear to disrupt LTB_4 and LXA_4 production as well as altering protection against naturally occurring *M. tuberculosis* infection. Together, these findings suggest that a combinatorial approach to tuberculosis therapy would be most effective, including antibiotics to help endogenous mechanisms kill the microorganism and SPMs to control the host immune response.

Sepsis

Sepsis is the most serious complication of acute bacterial infection. The host response in sepsis leads to diffuse systemic immune dysregulation that progresses rapidly, frequently resulting in shock. In Gram-negative bacteria-initiated sepsis, there appears to be a protective and potentially therapeutic role for lipid mediators. In mice with sepsis after caecal ligation and puncture, treatment with LXA_4 reduced the production of pro-inflammatory cytokines, while simultaneously promoting a reduction in Gram-negative bacteria loads that improved survival[95,96]. Resolvins also have an important protective role in sepsis models. RvD2 serves as a potent regulator of the systemic inflammatory response in sepsis[14]. This reduction in pro-inflammatory signals is a consequence, in part, of reduction in nuclear factor- κB (NF-κB) activity[13,60,96]. Treatment of septic mice with RvD2 leads to a profound reduction in the production of cytokines, including IL-6, IL-10 and interferon-α (IFNα), and leukocyte infiltration to the site of infection is reduced. Of interest, control of the inflammatory response leads to an overall reduction in bacterial loads, both at the local site of insult and systemically within the blood, and an improvement in overall animal survival[14]. Sepsis is a disease of overwhelming infectious insult, compounded by an overly robust inflammatory response, whereby treatment with anti-inflammatory therapies potentially subjects the host to further harm. Modulation of pro-resolution responses appears to promote dampening of the inflammatory response while still allowing for adequate, and possibly improved, clearance of the bacterial infection. The ability to clear the source of infection while still limiting the immune response provides an attractive therapeutic paradigm for this disease of substantial health-care burden.

The biological demand for an initial robust response against a bacterial insult is juxtaposed against the need to control prolonged and overly exuberant inflammatory responses that are potentially harmful, raising potential challenges for the therapeutic use of pro-resolving mediators. For example, in a pneumosepsis model, early treatment with LXA_4 appears to limit the immune response by decreasing leukocyte infiltration, reducing bacterial clearance and worsening the survival rate[97]. By contrast, in the same model, later treatment with LXA_4 had positive effects, allowing for adequate clearance of infection but dampening the protracted and pathological immune response, therefore enhancing survival[97]. In the future, timing and dosing considerations and concomitant antibiotic use will be important for developing SPM therapeutic strategies in sepsis.

Overall, in bacterial infection, SPMs have significant therapeutic potential with ongoing research focused on their anti-infective mechanisms and optimal dose and timing strategies to harness their beneficial actions. In animal models, the augmentation of resolution also appears to reduce the needed dosage for antibiotics in the clearance of bacterial infections[12,95]. Given the worldwide crisis of emerging antibiotic resistance, therapies that could reduce antibiotic usage provide an attractive alternative in the quest to develop new and enhanced antimicrobial therapeutic approaches.

SPMs in viral infections

Influenza

Viral pathogens also appear to interact with the host in a way that is modifiable by pro-resolving factors. Influenza viruses are a well-suited model to understand the role of resolution mediators and the mechanisms in viral infections, as different strains of the virus elicit varied host immune responses and outcomes. In studies that compare more virulent strains of the influenza virus to less virulent strains, pro-resolving mediators inversely correlated with biological activity of the virus. More virulent strains of influenza led to suppression of lipoxins[98], which is associated with enhanced viral dissemination. Protectin D1 has pivotal and multiple roles in regulating viral pathogenicity. More virulent influenza strains, such as H5N1, downregulate protectin D1 levels, and the pathogenicity of various isolates correlates inversely with levels of protectins[99]. In addition to host inflammatory responses, protectin D1 has direct antiviral actions on influenza; both protectin D1 and its isomer protectin DX (which is formed by LOX-mediated double oxygenation) interfere with viral RNA nuclear export machinery, thereby limiting viral replication[100–102]. Treatment of infected mice with protectin D1 improves survival (FIG. 4) even when administered as late as 48 hours after infection[102], at a time when current antiviral therapies are no longer significantly effective[103].

Respiratory syncytial virus

Respiratory syncytial virus (RSV) infection results in a bronchiolitis that is driven by classically activated macrophages and eventually resolved by alternatively activated macrophages[104]. Promotion of these two alternative macrophage fates appears related to RSV-induced COX2 (REF. 105) and LXA_4- and RvE1-mediated protective actions[106]. Host

responses to RSV again highlight roles for SPMs and lipid mediator class-switching in the initial control and eventual clearance of infection.

Herpes simplex virus

Herpes simplex virus (HSV) ocular infection represents another example in which local control of the virus results from a robust inflammatory response, with long-term consequences of chronic inflammation that persists after clearance of the virus, including the potential for eventual blindness from stromal keratitis. In animals with HSV, topical administration of RvE1 results in decreased influx of effector $CD4^+$ T cells (both T_H1 cells and T_H17 cells) and neutrophils, reduced production of pro-inflammatory cytokines, including IFNγ and IL-6, increased levels of the anti-inflammatory cytokine IL-10 and decreased pro-angiogenic factors[107]. Overall, RvE1 significantly decreased stromal keratitis. Similar results have been demonstrated for protectin D1 (REF. 108), further illustrating the potential therapeutic benefits of SPM control of pathogen-mediated inflammation to lessen injury to bystander tissues.

The interaction of the host immune system with infectious insults from viruses represents a novel opportunity for exploitation of SPMs. Finding the delicate balance between the need for a sufficient immune response to clear infection and rapid dampening of that response to prevent host damage is a well-suited target for SPMs, and further research is needed to identify opportunities for optimizing this balance in human viral infectious disease.

SPMs in parasitic infections

Responses to parasitic infections also appear to engage SPMs in host defence. With *Toxoplasma gondii*, there is a robust DC response with production of IL-12 (REF. 109). Lipoxins are generated *in vivo* during toxoplasmosis and act in an autacoid mechanism on DCs via ALX leading to reduction of CCR5 expression and diminished IL-12 production[110]. In animal models, 5-LOX deficiency results in the production of significantly more IL-2 and IFNγ compared with wild-type animals, as well as severe encephalitis and increased mortality, all of which can be reversed by administration of LXA_4 analogues[111]. Similar protective roles for lipoxins have been suggested for other intracellular and extracellular parasites, including *Angiostrongylus costaricensis*[112], *Plasmodium* spp.[113] and *Trypanosoma cruzi*[114].

Pathogen–host interactions for SPM biosynthesis

The generation of SPMs may not always be beneficial to the host. As discussed previously in *M. tuberculosis* infections, experimental models that strongly favour the generation of lipoxins over leukotrienes can have detrimental effects on pathogen clearance. If given early in pharmacologically large amounts, SPM regulation of the pathogen-mediated immune response may impair microbial clearance. In addition, there are now examples identified of select pathogens using local SPM production as an immune evasion and survival strategy. *T. gondii* is able to generate components of SPM biosynthetic pathways, resulting in local collaboration with host cells to increase lipoxin production with the consequence of a dampened immune response to *T. gondii* [115]. Recruitment of neutrophils, lymphocytes and

eosinophils to the site of infection are all decreased by this mechanism[115]. In addition to *T. gondii*, the opportunistic bacteria *Pseudomonas aeruginosa* can express a secreted LOX that can augment SPM production in the local milieu to modulate host defence[116]. Similarly, *Candida albicans* can biosynthesize RvE1 that limits IL-8-mediated neutrophil infiltration in the host, enabling colonization[117]. These examples further illustrate the delicate balance between the pathogen and the host in SPM production and control of host immune responses.

SPMs in chronic inflammatory diseases

Non-infectious inflammation is a common and often devastating cause of human disease. Most current therapies rely on blunting the inappropriate immune response through the use of anti-inflammatory medications, all of which have significant undesirable side effects, including increasing the host susceptibility to infection. Although the roles of SPMs have been investigated in many inflammatory diseases (TABLE 3), below we focus on the role of SPMs in inflammation of the lung by highlighting data from preclinical animal models.

Asthma and allergic inflammation

Asthma is a disease of excessive airway inflammation and hyperresponsiveness induced by irritant triggers and subsequently driven by a multitude of factors, including the trafficking of neutrophils, eosinophils and the generation of type 2 inflammatory responses in many cases. Severe asthma is poorly responsive to existing therapies, and it is characterized by increased oxidative stress and decreased lipoxin production in the airways[55,118,119]. Recently, the increased oxidative stress in uncontrolled asthma was linked to decreased lipoxin levels through a compensatory increase in soluble epoxide hydrolase activity[118]. As a consequence of the soluble epoxide hydrolase activity, levels of 14,15- epoxyeicosatrienoic acid levels were decreased, which adversely impacted lipoxin production[118], providing a biochemical mechanism for oxidative insults to disrupt lung resolution programmes. Low SPM levels in severe asthma are likely to have the functional consequence of chronic inflammation and airway hyperreactivity because airway LXA_4 blunts leukotriene- mediated bronchoprovocation in humans[120], and in mice stable analogues of LXA_4 block airway hyperresponsiveness, mucus metaplasia and type 2 lung inflammation[121,122], and accelerate resolution of the inflammatory response[73].

RvE1 has protective effects in preclinical models of allergic lung inflammation; it decreases eosinophil recruitment, type 2 cytokine production and airway hyperresponsiveness[73,123]. RvE1 targets NK cells in mouse models of asthma through the RvE1 receptor CMKLR1, promoting NK cell migration and cytotoxicity. With NK cell depletion, the pro-resolving function of RvE1 is partially impaired[68]. In allergic inflammation, RvE1 increases lipoxin formation, suggesting the possibility of redundant pathway effects to limit chronic inflammation. RvE1 inhibits IL-6, IL-23 and IL-17 release, thereby dampening the development and activation of T_H17 cells. Similarly to RvE1, lipoxins can inhibit IL-17 production but do not inhibit IL-23, which is indicative of convergent but not overlapping signalling pathways. Of note, as mentioned above, RvE1 and LXA_4 also engage distinct receptors, namely CMKLR1 and ALX, respectively[73]. RvD1 acts in a complementary

manner, similarly promoting the resolution of eosinophil tissue accumulation and pro-inflammatory responses with a macrophage directed action to enhance allergen phagocytosis and clearance[63]. Similarly, protectin D1 has been shown to promote resolution of the lung inflammatory response and block airway hyperresponsiveness[47]. Of interest, protectin D1 regulates IL-5 and IL-13 but not IL-4 levels, suggesting that ILC2s rather than T_H2 cells are likely to be a principal cellular target for protectin D1. It is notable that protectin D1 levels are decreased in exhaled breath condensates during asthma exacerbations[47].

Recently, lung sensory neurons were identified as early inducers of ILC2 activation in type 2 lung inflammation[124]. These activated neurons express transient receptor potential (TRP) channels, which can serve as SPM targets. Of note, mouse models have suggested a role for RvD1, RvE1, neuroprotectin D1 (NPD1) and MaR1 in attenuating pain by inhibition of TRP channels[125–128]. Because SPMs act at these pain receptors in the nervous system and on inflammatory pathways, these findings suggest that regulation of sensory neuron activation could be a crucial mechanism for SPM inhibition of both pain and lung inflammation. Together, these findings highlight an integrated network of pro- resolving mediators in asthma and allergic inflammation and suggest several potential therapeutic targets.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a pulmonary inflammatory disease most often triggered by cigarette smoke and propagated through maladaptive and prolonged pro-inflammatory responses, predisposing the host to recurrent infections. Pro-inflammatory lipid mediators, including leukotrienes, have been observed at elevated levels in patients with COPD[119]. Roles for SPMs remain to be determined in these individuals. In addition to LXA_4, the acute phase reactant serum amyloid A (SAA) can also interact with ALX, and it is increased in COPD exacerbations[27], which are largely caused by viral and bacterial respiratory tract infections. In acute exacerbations of COPD, levels of SAA are more than 2 log orders higher than LXA_4 (REF. 27). In sharp contrast to LXA_4, when SAA engages ALX, it triggers a pro- inflammatory, neutrophil driven response. Although SAA-mediated inflammation is glucocorticoid-resistant, it can be regulated by pharmacological dosing of lipoxins[27], suggesting a new therapeutic approach for steroid-resistant lung inflammation.

The role of resolvins in COPD is a subject of active investigation. Cigarette smoke exposure results in the development of classically activated macrophages, which produce a pro-inflammatory response. Alternatively activated, or M2, macrophages also play a part in the clearance of inhaled particles and quelling of the initial response to the cigarette smoke. RvD1 polarizes cigarette smoke-exposed macrophages towards the M2 pathway, resulting in enhanced phagocytosis as well as upregulated production of IL-10 (REF. 64). RvE1 also acts on cigarette smoke-activated macrophages, reducing superoxide production and limiting inflammation[129]. The ability of resolvins to polarize the macrophage population towards the M2 phenotype suggests a novel mechanism for SPM control in this chronic inflammatory disorder.

Cystic fibrosis

Cystic fibrosis is a genetic disorder with multi-organ defects caused by a single mutation. Patients with cystic fibrosis have viscous respiratory tract secretions, recurrent airway infections and an over-exuberant immune response, eventually resulting in the deterioration of lung function. Genetic modifier analysis suggests that patients with cystic fibrosis who carry a polymorphism in *PTGS2* (encoding COX2) that leads to reduced production of pro-inflammatory mediators have improved clinical status[130]. Profiling of lipid mediators in the airways of patients with cystic fibrosis showed that lipoxin levels may be lower in these patients compared with healthy control subjects[54]. Moreover, patients with cystic fibrosis who had detectable levels of RvE1 in the airways showed improved lung function compared with patients without any detectable RvE1 (REF. 131). Furthermore, in animal models of cystic fibrosis, lipoxin administration suppresses neutrophil infiltration and reduces bacterial burden, resulting in an overall reduction in disease severity[54].

Fibrotic lung disease

Multiple pulmonary injurious exposures have a unifying endpoint in the development of extensive tissue scarring, resulting in poor gas exchange, air movement and demise of the host. These fibrotic lung diseases can be mediated by a poorly controlled inflammatory response that triggers a fibrotic response in a mal-adaptive attempt to heal the damaged lung parenchyma. These diseases represent a devastating human burden, as very few treatments exist to slow or reverse this fibrotic process. Pro-resolving mediators could represent a novel strategy in a sparse arsenal. Bleomycin is an important chemotherapeutic agent but carries a known risk of pulmonary fibrosis. Treatment with LXA_4 or 15-epi-LXA_4 results in an attenuation of pulmonary fibrosis in animals exposed to bleomycin through reduction of the pro-fibrotic cytokine TGFβ[132], as well as an increase in the prevalence of M2 macrophages[133], both resulting in decrease fibrotic matrix and improved pulmonary function. In humans, scleroderma lung disease is characterized by idiopathic progressive lung inflammation and fibrosis and, of interest, patients with scleroderma lung disease underproduce pro-resolving mediators, in comparison to their pro-inflammatory counterparts[134].

Acute respiratory distress syndrome

ARDS is a prevalent condition with high rates of morbidity and mortality. It is characterized by an overly robust inflammatory response to infection (for example, pneumonia and sepsis) or injury that fills the alveoli with oedema and pus, resulting in life-threatening respiratory failure. Many unsuccessful attempts have been made to therapeutically target an inflammatory pathway to limit this over-exuberant host response. In contrast to these anti-inflammatory strategies, a pro-resolving therapeutic strategy directed at harnessing host pro-resolving mechanisms is showing promise in preclinical model systems. Using a sterile model of ARDS from gastric acid aspiration, an important clinical risk factor for ARDS, several SPMs, including LXA_4, 15-epi-LXA_4, RvE1, RvD1 and MaR1, have proven effective as pharmacological agents in limiting acute lung inflammation and injury, and accelerating lung tissue catabasis[13,29,59,60,135]. Because SPMs engage endogenous resolution pathways, these mediators have the potential to both decrease pathogen-mediated

inflammation and enhance host defence, which distinguishes SPMs from immunosuppressive agents. Early inflammation in ARDS is mediated by platelet–neutrophil interactions[59,136], and this interaction can lead to transcellular production of lipoxins or of the most recently discovered member of the SPM family, MaR1 (REF. 59). Treatment with MaR1 is organ protective and limits the extent of lung inflammation. Furthermore, the timing of MaR1 production appears specific and regulated, as does the production of RvD1 (REF. 137). Together, these findings highlight the potential roles SPMs could have in decreasing the severity and duration of ARDS and, more generally, the data support a targeted pro-resolving approach as a new therapeutic strategy for this devastating condition that is currently without available medical treatment.

Human translation

As momentum grows to leverage these natural resolution pathways for rational new therapeutic strategies for diseases of acute and chronic inflammation, it is essential to clarify the roles of SPMs in human host defence and in the regulation of pathogen-mediated inflammation. As discussed above, preclinical data for bacterial infection points to important and pivotal roles for lipid mediators, in particular SPMs, in the regulation of host responses to infection[12,13] with the potential for host SPM-directed interventions to decrease antibiotic requirements[12,95]. In addition, for viral host responses, SPMs lessened the severity of influenza and HSV infections[102,107,108]. Several lines of evidence have suggested dysregulation of SPM pathways in several human diseases[27,47,55].

Clinical trials with SPM analogues that resist metabolic inactivation are still in early phases. A recent study of children with infantile eczema compared a topical stable LXA_4 analogue (15-(*R/S*)-methyl-LXA_4) to the current clinical approach of topical corticosteroids (specifically, mometasone). 15-(*R/S*)-methyl-LXA_4 was well tolerated and controlled clinical symptoms and disease as effectively as topical steroids[138]. This trial is the first to report successful treatment with an SPM in humans. Moreover, for allergic diseases, inhaled LXA_4 decreases LTC_4-initiated bronchoprovocation in patients with asthma[120]. Several clinical trials using a topical formulation of an RvE1 analogue for ocular conditions are also underway (NCT01639846, NCT01675570, NCT00799552 and NCT02329743).

Conclusion

Host responses to infection naturally trigger both an acute inflammatory response and its resolution. Counter-regulation of pathogen-mediated inflammation is an active process with specific cellular and biochemical events that are tightly regulated in health. With the identification of several families of endogenous pro-resolving mediators, their potent anti-inflammatory properties are now being determined. Distinct from immunosuppressive agents, these endogenous pro-resolving mediators generally display protective actions in host defence, including direct antimicrobial actions. There is still much to be done to more fully understand the intersection of these novel endogenous pathways in control of pathogen-mediated inflammation and the diversity of their mechanisms in microbial pathogenesis. The abundant presence of SPMs in human healthy breast milk[139] suggests important protective actions for these mediators. Clinically, acute infections are principally

treated with antibiotics with current approaches devoid of host-directed therapy. In light of the current serious threat of emerging pathogens, in particular those that display antibiotic resistance, the development of therapies to augment host anti-infective mechanisms are needed. Members of the growing new genus of SPMs or their bioactive stable analogues represent potential candidates to harness endogenous anti-inflammatory resolution mechanisms to limit overly exuberant pathogen-mediated inflammation in future therapeutic strategies.

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Glossary

Catabasis	An active process at the cellular and tissue level governed by specific mediators that promote a return to tissue homeostasis
Efferocytosis	The cellular process by which phagocytes engulf dying and dead cells (for example, apoptotic or necrotic) for removal from tissues. It is part of the resolution programme to restore tissue homeostasis

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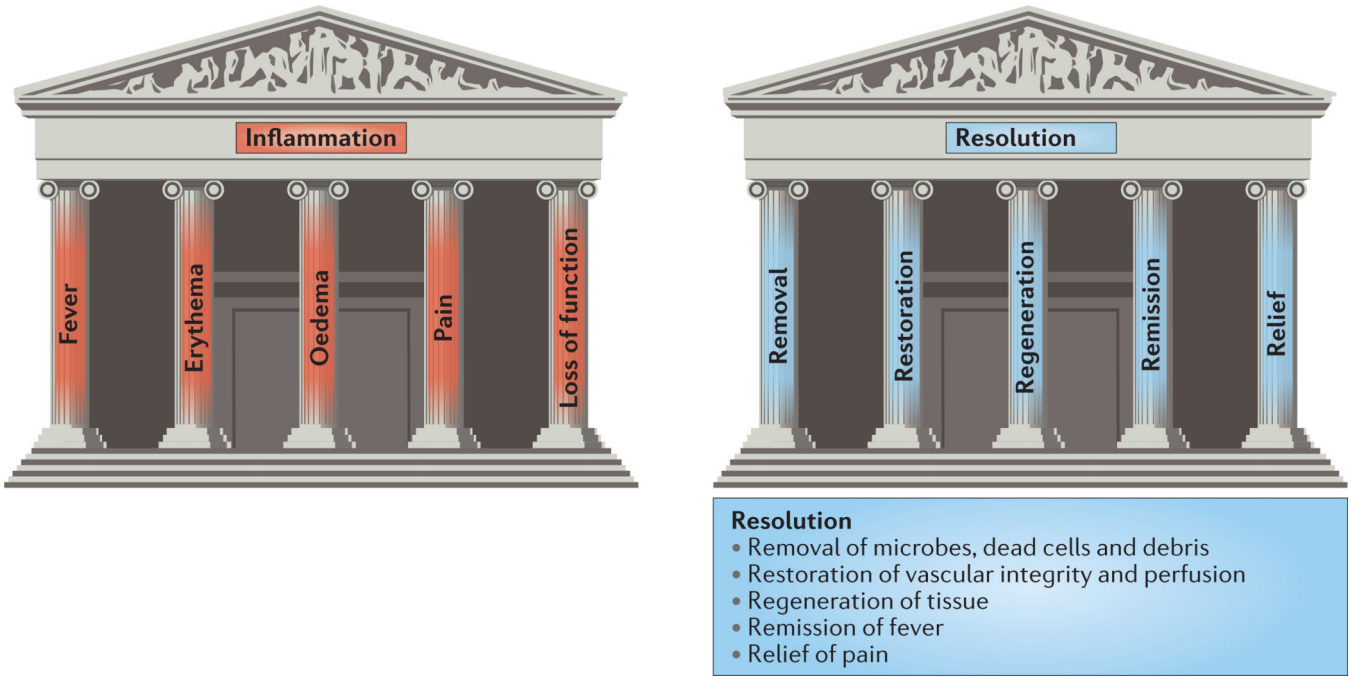

Figure 1. Cardinal signs of inflammation and its resolution

Tissue- and organism-level responses to inflammation have been well recognized for centuries and can be summarized as the ‘five pillars of inflammation’; namely, *calor* (fever), *rubor* (redness), *tumor* (swelling and oedema), *dolor* (pain) and *functio laesa* (loss of function). With the recognition that the resolution of inflammation is an active process, recent research has identified molecular and cellular processes that promote catabasis. These can be summarized as the ‘five pillars of resolution’; that is, removal of microorganisms, dead cells and debris, restoration of vascular integrity and perfusion, tissue regeneration, remission of fever and relief from inflammatory pain.

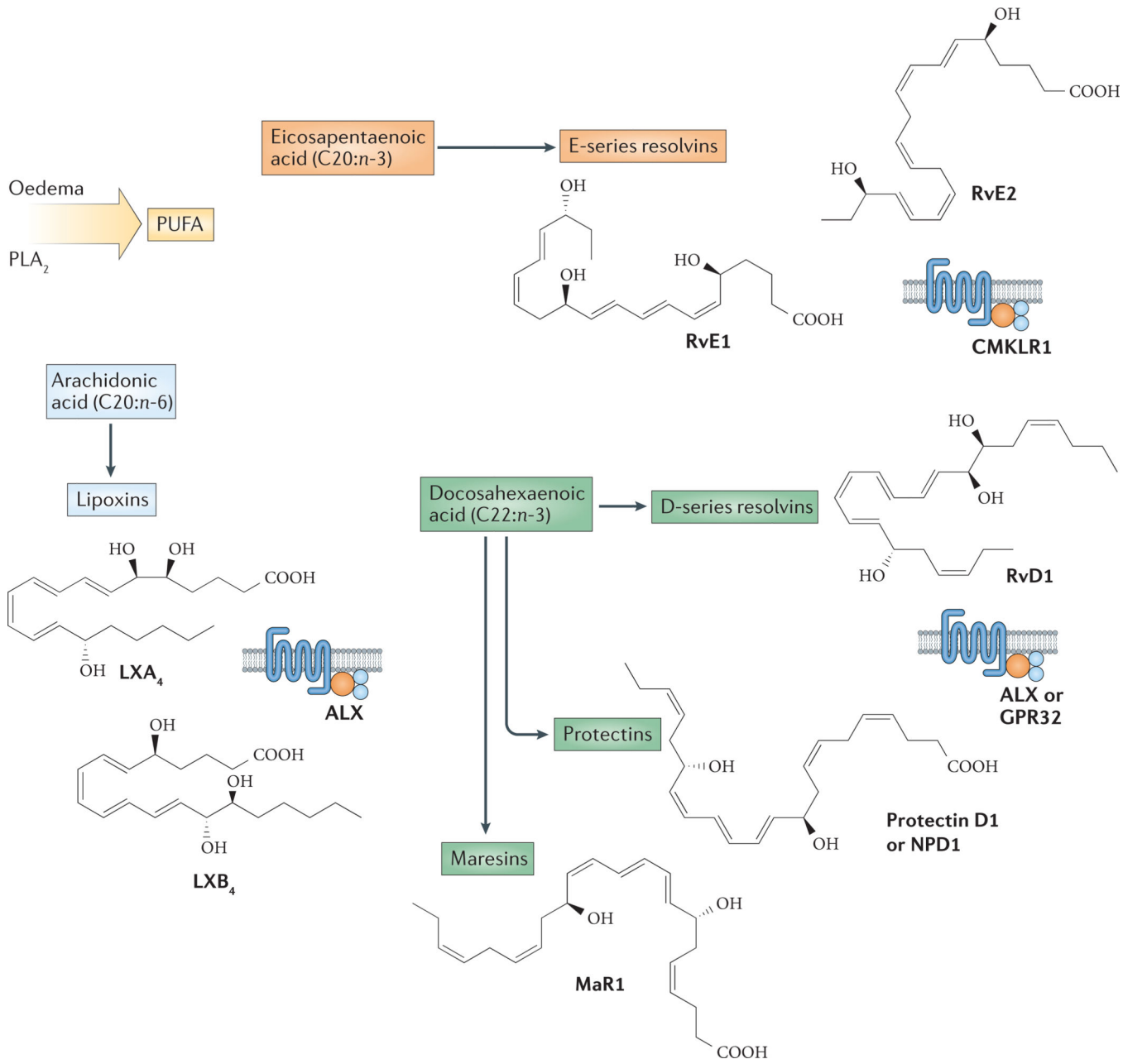

Figure 2. Polyunsaturated fatty acids are substrates for specialized pro-resolving mediators

Stereoselective mediators that enhance host defence, resolve tissue inflammation and stimulate tissue regeneration have been described[4]. These specialized pro-resolving mediators (SPMs) are produced in a spatio-temporally regulated manner from essential polyunsaturated fatty acids (PUFAs) that are either released enzymatically by phospholipase A_2 (PLA_2) from cell membranes for secondary conversion by biosynthetic enzymes or delivered with oedema fluid from plasma to exudates. The principal SPM families are lipoxins from arachidonic acid (C20:4*n*-6; in light blue), as well as the E-series resolvins from eicosapentaenoic acid (C20:5*n*-3; in pink) and D-series resolvins, protectins and maresins from docosahexaenoic acid (C22:6*n*-3; in green). The SPM precursors

eicosapentaenoic acid and docosahexaenoic acid are essential omega-3 PUFAs. Representative members of these families, their structures and receptors are shown here. CMKLR1, chemokine-like receptor 1; GPR32, probable G protein-coupled receptor 32; LX, lipoxin; MaR1, maresin 1; NPD1, neuroprotectin D1; RvD1, resolvin D1; RvE, resolvin E.

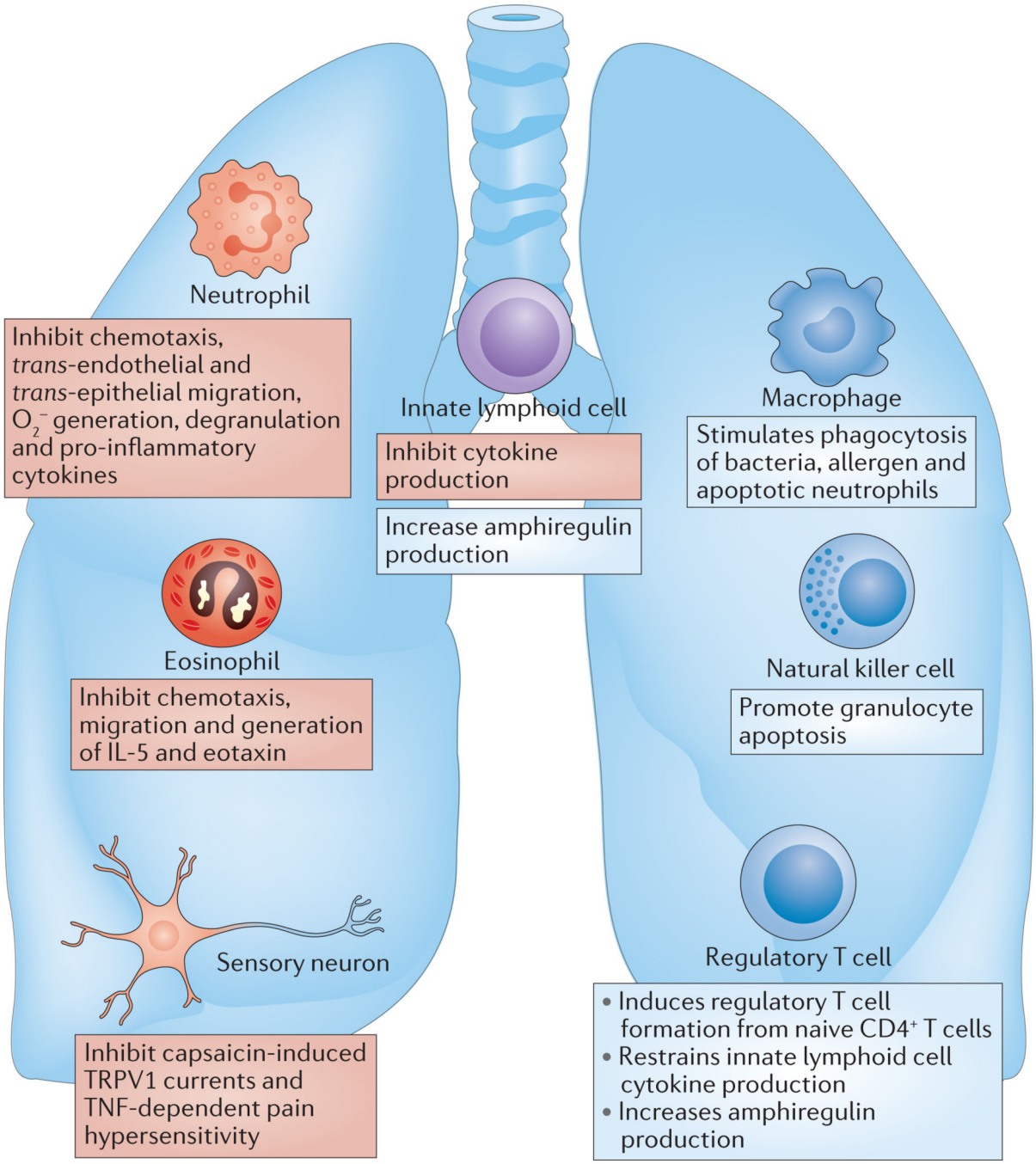

Figure 3. Cellular mechanisms for SPMs in lung anti-inflammation and pro-resolution

During a self-limited inflammatory response, resolution of inflammation is an active process governed by specialized pro-resolving mediators (SPMs) that transmit both anti-inflammatory (red) and pro-resolving (blue) actions to leukocytes and tissue-resident cells. This class of endogenous immunoresolvents induces an anti-inflammatory response by inhibiting granulocyte migration and activation, disrupting sensory neuron activation and dampening cytokine production by a variety of structural cells, including epithelial cells, endothelial cells and fibroblasts. SPMs have a multipronged action to regulate sentinel

innate lymphoid cells to decrease cytokine and increase amphiregulin production. These mediators also promote resolution by inducing regulatory T cells to control innate lymphoid cells, stimulating natural killer cells to trigger granulocyte apoptosis and engaging macrophages in a non-phlogistic manner to engulf bacteria and noxious stimuli, and clear apoptotic cells by efferocytosis. IL-5, interleukin-5; O_2, superoxide; TNF, tumour necrosis factor; TRPV1, transient receptor potential cation channel subfamily V member 1.

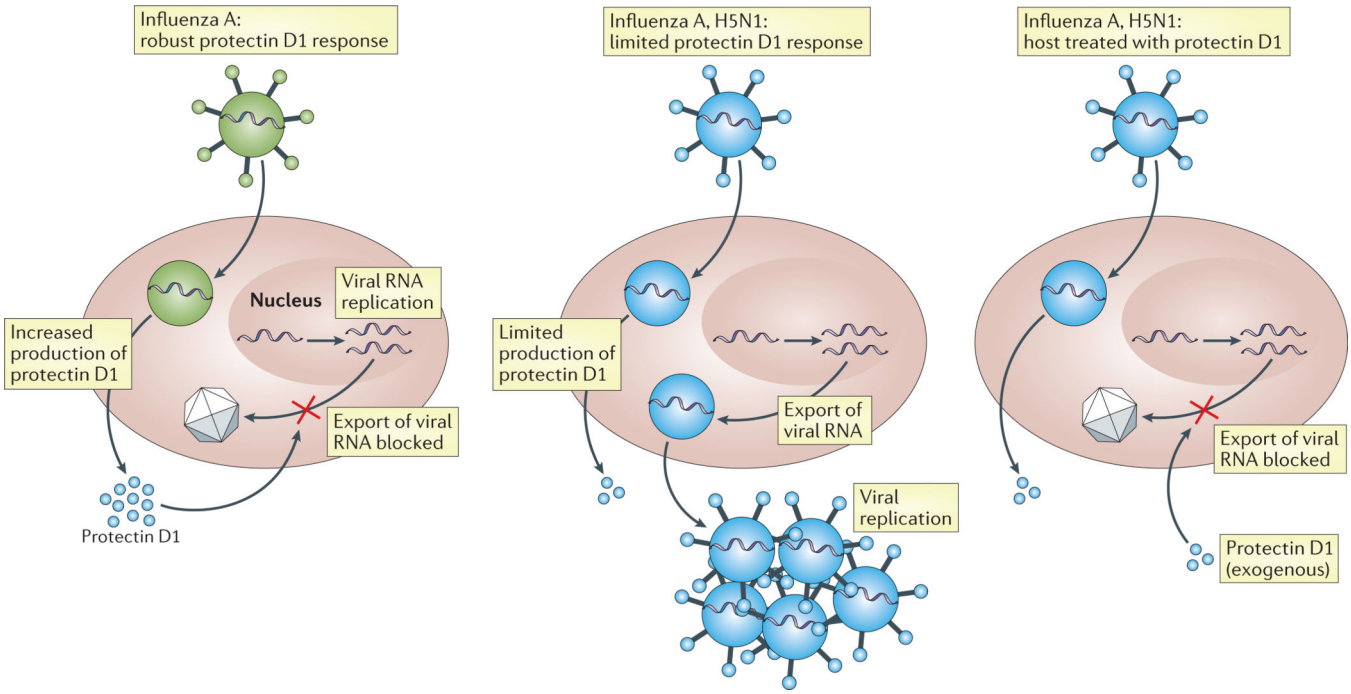

Figure 4. Selected SPMs increase antiviral host defence

In hosts infected with influenza viruses, endogenous protectin D1 production is increased. Protectin D1 limits influenza pathogenicity by directly interacting with the RNA replication machinery to inhibit viral RNA nuclear export. In particularly virulent strains of influenza, such as the H5N1 avian (A) strain, protectin D1 formation is not sufficiently upregulated, leading to more efficient viral replication and host demise. Treatment of the host with exogenous protectin D1 can restore inhibition of viral RNA export, thereby limiting viral replication and improving host survival.

Table 1

SPMs display cell-type specific actions

Mediator	Target cell	Action(s)	Refs
Lipoxin A_4	Neutrophil	Inhibits chemotaxis, *trans*-endothelial and *trans*-epithelial migration	140, 141
		Inhibits neutrophil–epithelial cell interactions	75, 77, 140
		Inhibits superoxide anion generation and degranulation	142,144
	Monocyte	Stimulates chemotaxis and adhesion	145
		Inhibits peroxynitrite generation	146
		Reduces IL-8 release by cells from individuals with asthma	147
	Macrophage	Increases engulfment of apoptotic neutrophils	62
	Eosinophil	Inhibits migration and chemotaxis	148
		Inhibits generation of eotaxin and IL-5	112
	NK cell	Inhibits NK cell cytotoxicity	149
		Increases granulocyte apoptosis	67
	ILC2	Inhibits IL-13 release	67
	Dendritic cell	Inhibits IL-12 production	110
	Epithelial cell	Increases proliferation after acid injury, blocks IL-6 and IL-8 release	77
	Endothelial cell	Stimulates PKC-dependent prostacyclin formation	150
		Blocks the generation of reactive oxygen species	151
		Inhibits VEGF-induced endothelial-cell migration	152
	Fibroblast	Inhibits IL-1β-induced IL-6, IL-8 and MMP3 production	153
		Inhibits CTGF-induced proliferation	154
	Smooth muscle	Inhibits LTC_4-initiated migration	155
Resolvin E1	Neutrophil	Inhibits *trans*-epithelial and *trans*-endothelial migration	156
		Inhibits superoxide generation	87
	Macrophage	Stimulates non-phlogistic phagocytosis of apoptotic neutrophils	30
	Dendritic cell	Inhibits IL-12 production	157
		Inhibits migration	41
	NK cell	Expresses CMKLR1 receptors	67
Resolvin E3	Neutrophil	Inhibits infiltration	158
Resolvin D1	Neutrophil	Inhibits transmigration	159
	Macrophage	Inhibits LPS-induced TNF release	160
		Increases phagocytosis of allergen and apoptotic cells	9,63
Protectin D1	Neutrophil	Inhibits TNF and IFNγ release	161
		Inhibits PMN transmigration	11
		Upregulates CCR5 expression	72
	Macrophage	Stimulates non-phlogistic phagocytosis of apoptotic PMNs	30
Maresin 1	ILC2	Inhibits IL-13 production and stimulates amphiregulin production	70
	Regulatory T cell	Induces regulatory T cell formation and stimulates amphiregulin production	70

Mediator	Target cell	Action(s)	Refs
	Bronchial epithelial cell	Inhibits organic dust-induced cytokine production	162

CCR5, CC-chemokine receptor 5; CMKLR1, chemokine-like receptor 1; CTGF, connective tissue growth factor; IFNγ, interferon-γ; IL, interleukin; ILC2, group 2 innate lymphoid cell; LPS, lipopolysaccharide; LTC_4, leukotriene C_4; MMP3, matrix metalloproteinase 3; NK, natural killer; PKC, protein kinase C; PMN, polymorphonuclear leukocyte; SPM, specialized pro-resolving mediator; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor.

Table 2

SPMs influence host defence and infectious inflammation

Infection or infective agent	Mediator	Role	Refs
Virus			
Influenza A	Lipoxins	H5N1, a more virulent strain, is associated with a decrease in lipoxin signalling leading to increased leukocyte recruitment and extrapulmonary dissemination of the virus	98
	Protectins	Protectin D1 is suppressed in virulent H5N1; treatment with protectin D1 improves survival	102
RSV	Lipoxins	Lipoxins are required to elicit alternatively activated macrophages, leading to resolution of lung pathology	106
HIV	Lipoxins	Lipoxins are produced in HIV infection, but their function is uncertain	163
HSV	Resolvins	Reduce neutrophil and $CD4^+$ T cell recruitment (T_H1 cells and T_H17 cells), increase IL-10 and decrease pro-inflammatory cytokines and stromal keratitis lesions	107
	Protectins	Reduce neutrophil and $CD4^+$ T cell recruitment (T_H1 cells and T_H17 cells), increase IL-10 and decrease pro-inflammatory cytokines and stromal keratitis lesions	108
Bacterial infection			
Mycobacterium tuberculosis	Lipoxins	5-lipoxygenase deficient mice have lower circulating levels of LXA_4 increased T_H1-type inflammation and lower rates of resistance	92
		LXA_4 associates with plasma membrane repair and necrosis of infected macrophages	164, 165
		Mycobacterial susceptibility is linked to LTA_4 hydrolase activity that controls LTB_4 production directly and LXA_4 production indirectly	15
		Variations in the *ALOX5* gene (which encodes 5-lipoxygenase) are associated with variation in tuberculosis susceptibility	93
Periodontitis	Lipoxins	In rabbits, overexpression of lipoxin or treatment with a lipoxin analogue decreases bone loss and tissue inflammation	85
		Decrease PMN infiltration to sites of *Porphyromonas gingivalis* infection	84
		LXA_4 analogue promotes regeneration of hard and soft tissue loss in pig models of periodontitis	166
	Resolvins	Resolve local inflammation and promote tissue regeneration after infection-mediated destruction	61
		Decrease inflammation and protect against bone loss	87
		Decrease neutrophil infiltration and pro-inflammatory cytokine levels	88
		Restore impaired phagocyte activity of macrophages	90
		RvE1 is bone-protective in murine models, mediating preservation and accelerating regeneration	167
Salmonella spp.	Lipoxins	Increase BPI and enhanced bacterial killing	79
Gram-negative bacteria-associated sepsis	Lipoxins	Decrease pro-inflammatory mediators via NF-κB mediated mechanism, decrease bacterial load and increase peritoneal macrophages and survival	96
		Decrease PMN recruitment, attenuate inflammation and, in combination with antibiotics, improve survival	95
	Resolvins	Decrease bacterial burden, limit cytokine production, increase macrophage phagocytosis and improve survival	14
		Decrease antibiotic requirements, enhance actions of ciprofloxacin and accelerate resolution	12

Infection or infective agent	Mediator	Role	Refs
Burn-associated sepsis	Resolvins	Enhance and/or restore neutrophil recruitment and improve overall survival	168
Escherichia coli (pneumonia and ARDS)	Lipoxins	Promote apoptosis of neutrophils	80
	Resolvins	Decrease neutrophil recruitment, enhance bacterial clearance, decrease IL-1 and IL6, and improve survival	13
		Enhance neutrophil apoptosis and improve survival	81
Staphylococcus aureus	Resolvins	Enhance vancomycin-mediated clearance of bacteria	12
Borrelia burgdorferi	Lipoxins	In the absence of 5-lipoxygenase, mice develop persistent arthritis	91
Parasites			
Toxoplasma gondii	Lipoxins	Infected mice have high serum levels of lipoxins	115
		5-lipoxygenase deficient animals have higher levels of IL-12 and IFNγ with improved parasite control but have higher mortality from excess inflammation	111
		LXA_4 suppressed IL-12 production in dendritic cells	110
Trypanosoma cruzi	Lipoxins	Aspirin-triggered lipoxins are elevated, and increased 15-epi-LXA_4 levels improve parasite load, cardiac inflammation and mortality	114
Plasmodium spp. (malaria parasite)	Lipoxins	5-lipoxygenase deficient mice have higher levels of IL-12 and IFNγ and increased mortality. Treatment with lipoxins decreases brain inflammation and improves survival	113
Angiostrongylus costaricensis	Lipoxins	Treatment of infected rats with an LXA_4 analogue shortens the duration of the allergic response to the parasitic infection	112
Yeast			
Candida albicans	Resolvins	Reduces neutrophil chemotaxis, enhances phagocytosis and promotes clearance	117

ARDS, acute respiratory distress syndrome; BPI, bactericidal permeability-increasing protein; HSV, herpes simplex virus; IFNγ, interferon-γ; IL, interleukin; LT, leukotriene; LXA4, lipoxin A4; NF-κB, nuclear factor-κB; PMN, polymorphonuclear leukocyte; RSV, respiratory syncytial virus; RvE1, resolvin E1; SPM, specialized pro-resolving mediator; T_H, T helper.

Table 3

Roles for SPMs in non-pulmonary settings

Disease or procedure	Mediator	Role	Refs
Murine models of organ transplantation	Lipoxins	Lipoxin analogue and increased LXA_4 receptor expression prolong orthotopic heart transplant survival	169
		Lipoxin prevents acute rejection after liver transplantation	170
	Resolvins	RvE1 prolongs survival of vascularized renal transplant	169
		RvD1 analogue prolongs corneal transplant survival	171
Graft versus host disease	Lipoxins	LXA_4 and 15-epi-LXA_4 administration improves clinical symptoms	172
Alzheimer disease	Lipoxins	LXA_4 decreases NF-κB expression and recruits microglia, promoting clearance of amyloid-β deposits and improving cognition in mouse models	173
	Protectins	NPD1 promotes brain cell survival and an anti-apoptotic gene expression programme in human tissue	174
	Resolvins	RvD1 stimulates macrophage phagocytosis of amyloid-β *in vitro* in PBMCs from patients with Alzheimer disease	175
Amyotrophic lateral sclerosis	Resolvins	RvD1 inhibits IL-6 and TNF production in macrophages derived from post mortem samples	176
Murine models of inflammatory bowel disease or colitis	Lipoxins	15-epi-LXA_4 enhances phagocytic clearance of bacteria and limits the inflammatory cytokine milieu	177
		LXA_4, through NF-κB, downregulates pro-inflammatory cytokines and improves mortality	178
	Resolvins	RvE1 suppresses pro-inflammatory response of macrophages	179
		RvE1 blocks leukocyte inflammation and protects against colitis	157
		RvD2 and AT-RvD1 decrease neutrophil infiltration and cytokine response, and improves clinical metrics	180
Diabetes	Resolvins	RvD1 improves glucose tolerance and insulin sensitivity associated with obesity-induced diabetes in mice	181
		The RvD1 precursor 17-HDHA reduces adipose tissue inflammation and improves glucose tolerance in mouse models	182
Chronic pancreatitis	Resolvins	RvD1 limits inflammation in the dorsal horn, limiting allodynia in rat models	183
Murine models of corneal healing	Lipoxins	LXA_4 and protectin D1 improve corneal healing and limit tissue injury	184
	Resolvins	RvE1 limits goblet cell loss in chronic dry eye	185
		RvE1 improves goblet cell function and tear formation and limits inflammation	186–188
Retinopathy	Resolvin and protectins	RvD1, RvE1 and protectin D1 all protect against revascularization in mouse models	189
Glomerulonephritis	Lipoxins	Lipoxin upregulation promotes preservation of function in experimental glomerulonephritis	190
Renal fibrosis	Lipoxins	LXA_4 limits collagen deposition and promotes IL-10 while inhibiting pro-inflammatory cytokines in rat models	191
	Resolvins	In mouse models of ischaemia–reperfusion injury, RvD1 restores function, reduces infiltration of leukocytes and blocks macrophage activation	160
		RvE1 inhibits fibroblast proliferation in mouse post-obstruction injury models	192

Disease or procedure	Mediator	Role	Refs
	Protectins	In ischaemia–reperfusion injury, protectin D1 restores function, reduces infiltration of leukocytes and blocks macrophage activation	160
Arthritis	Lipoxins	LXA_4 resolves inflammation mediated by PGE_2 in mouse models of autoimmune arthritis	52
		LXA_4 receptor agonist decreases histological joint destruction and decreases clinical severity in murine collagen-induced arthritis	193
	Resolvins	RvD1 and AT-RvD1 improves hyperalgesia through modulation of NF-κB and COX2 in dorsal root ganglia in rat models of arthritis	194
Cardiac reperfusion Injury	Resolvins	RvE1 is cardioprotective and limits infarct size in rat cardiac ischaemia models	195
Atherosclerosis	Lipoxins	Overexpression of 15-lipoxygenase protects against lipid deposition and limits plaque development in rabbit transgenic models	196
Ischaemic stroke	Resolvins	AT-Resolvins are neuroprotective and limit leukocyte infiltration in mouse stroke models	197
Atopic dermatitis	Resolvins	RvE1 improves skin lesions through reduction of IL-4, IFNγ and eosinophill infiltration in murine models	198
Fibromyalgia	Resolvins	RvD2 and AT-RvD1 inhibit allodynia and limit depressive symptoms in a mouse disease model	199
Inflammatory pain in murine models	Resolvins	RvD1 limits pain and reverse thermal and mechanical injury in inflamed tissue	200
		RvE1 limits inflammation, as well as heat and mechanical pain	128
	Protectins	Protectin D1 inhibits capsaicin-induced TRPV1 currents and TNF-dependent pain hypersensitivity	125
	Maresins	MaR1 inhibits capsaicin-induced TPRV currents and reduces inflammation and chemotherapy-induced pain	127

17-HDHA, 17-hydroxy docosahexaenoic acid; AT, aspirin-triggered; COX2, cyclooxygenase 2; IFNγ, interferon-γ; IL-4, interleukin-4; LXA_4, lipoxin A_4; MaR1, maresin 1; NF-κB, nuclear factor-κB; NPD1, neuroprotectin D1; PBMC, peripheral blood mononuclear cell; PGE_2, prostaglandin E_2; RvD, resolvin D; RvE1, resolvin E1; SPM, specialized pro-resolving mediator; TNF, tumour necrosis factor; TRPV, transient receptor potential cation channel subfamily V.