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The Resolution Code of Acute Inflammation: Novel Pro-Resolving Lipid Mediators in Resolution

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Abstract

Studies into the mechanisms in resolution of self-limited inflammation and acute reperfusion injury have uncovered a new genus of pro-resolving lipid mediators coined specialized pro-resolving mediators (SPM) including lipoxins, resolvins, protectins and maresins that are each temporally produced by resolving-exudates with distinct actions for return to homeostasis. SPM evoke potent anti-inflammatory and novel pro-resolving mechanisms as well as enhance microbial clearance. While born in inflammation-resolution, SPM are conserved structures with functions discovered in microbial defense, pain, organ protection and tissue regeneration, wound healing, cancer, reproduction, and neurobiology-cognition. This review covers these SPM mechanisms and other new omega-3 PUFA pathways that open their path for functions in resolution physiology.

Keywords

inflammation; host defense; infection; essential fatty acids; lipid mediator

1. Introduction

The origins of resolving inflammation trace to the 11th century in the Canon of Medicine [1] as a *resolvent* promotes the disappearance of inflammation. For historical perspective on resolution, interested readers are directed to ref. [1] for a recent review. Barrier break, trauma and microbial invasion each create the host's need to neutralize invaders, clear the site, remodel and regenerate tissue (Fig. 1A); the inflammatory response is a terrain where lipid mediators (LM) such as eicosanoids (prostaglandins (PG) and leukotrienes (LT)) [2]

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and novel pro-resolving mediators uncovered [3, 4] play pivotal roles. The acute inflammatory response is divided into initiation and resolution phases (Fig. 1A).

Leukocyte traffic from circulation forms inflammatory exudates traditionally viewed as a battlefield. The first responders, neutrophils (PMN), swarm like sharks to defend the host along chemotaxic gradients, e.g. LTB_4 [5, 6], exiting venules governed by PGE_2 and PGI_2 and influx to form the exudate. The main events in resolution are cessation of PMN influx and macrophage clearance of debris. *But how does the host return the system to homeostasis and what are the roles of chemical mediators and the inflammatory exudate in timely resolution?*

Excessive inflammation is widely appreciated as a unifying component in many chronic diseases including vascular diseases, metabolic syndrome, neurological diseases, and many others, and thus a significant public health concern. Since the acute inflammatory response is protective, evolved to permit repair of injured tissues and eliminate invading organisms, it is *ideally self-limited* and leads to complete resolution enabling return to homeostasis (Fig. 1A). Although resolution of disease is appreciated by clinicians, resolution was considered a *passive* process [7], passive in that the chemoattractant and other chemical mediators involved in mounting the inflammatory response would just dilute and dissipate [8, 9]. With identification of proresolving mediators, we obtained evidence *that resolution of self-limited inflammation is an active programmed response* that *is "turned on" and not simply a process of diluting chemoattractant gradients*. Unexpectedly, n-3 PUFA present in marine oils are precursors of proresolving mediators (Fig. 1A&B).

Since n-3 PUFA EPA and DHA have cardioprotective and anti-inflammatory effects, they were held earlier to simply compete with arachidonic acid for eicosanoid biosynthesis, preventing pro-inflammatory eicosanoids, a process readily discernible in vitro [10]. Utilization of n-3 PUFA by resolving exudates to biosynthesize novel pro-resolving local mediators -- resolvins, protectins and maresins, collectively coined SPM, which potently stimulate cessation of PMN infiltration and enhance macrophage uptake of apoptotic cells, debris and microbes -- has opened a new focus on resolution pathways and innate immune mechanisms to attain homeostasis (Fig. 1B). This review focuses on the role of LM in resolution that now function in other systems including host-defense, nervous, reproductive, and muscle and exercise, giving promise for SPM, their pathways and related products in resolution physiology and pharmacology.

2. Elucidation of Pro-Resolving LM and the Newest Additions RvD3 and MaR1 Pathway

Key to this recent ***paradigm change*** is identification of novel families of autacoids that include *resolvins, protectins*, their aspirin-triggered forms and maresins, providing evidence that resolution is orchestrated by LM (Fig. 2 and Box 1). From this, it's evident that resolution programs of acute inflammation hold promise and remain largely uncharted [7] (Fig. 1). Challenges ahead are whether we can harness these novel LM that *stimulate* resolution (i.e. agonists of resolution coined **resolvents** [1, 11, 12]) and their resolution mechanisms. Dietary n-3 supplements are widely used, but <25% are directed by health care

providers [13]. Clinical trials with n-3 PUFA show mixed results [14], suggesting *that fatty acids themselves are not highly suitable to consider as drugs, given their many metabolic fates in humans*. Hence, it is critical for public health to establish mechanisms that underlie their essential health requirements.

Box 1

Specialized Proresolving Mediators (SPM): Anti-Phlogistic Pro-Resolving Actions (see Figure 1, Panel B)

SPM Defining Bioactions

- Temporal biosynthesis with leukocyte exudate traffic
- Cessation of PMN infiltration; Stop signals to limit further PMN recruitment and PMN-mediated tissue damage
- Enhance macrophage phagocytosis of apoptotic PMN, cellular debris and bacteria killing
- SPM possess broad anti-inflammatory & pro-resolving actions at both transcriptional and translational levels

Counter-regulate & Reduce Cardinal Signs of Inflammation

- Prostaglandins (COX-2 expression) and leukotrienes (LTB_4, LTC_4, LTD_4)
- PAF formation and actions
- Chemokines and cytokines (TNFα, IL-1β, IL-6, IL-8, IL-12, etc.)
- NFκB associated gene products
- Growth factors (VEGF)
- Extracellular ROS
- Edema

Activate

- Local NO, PGI_2 production via endothelial cells
- Heme oxygenase (HO-1) induction
- Macrophage phagocytosis (bacteria, microbial particles) and efferocytosis (apoptotic cells)
- Macrophage IL-10 production
- Enhance PMN phagocytosis, phagolysosomal ROS, microbial killing and clearance
- IL-1ra production
- Adiponectin

Using a systems approach with resolving exudates, we elucidated new essential PUFA-derived SPM pathways [4, 15]. Their biosynthesis and complete stereochemistry of each major resolvin (RvE1, RvD1, RvD2, RvD3 and RvD5) and protectin -- their potent bioactions (reviewed in [16]), now independently confirmed by many worldwide -- are the focus of increasing interest given that SPM control the magnitude and duration of inflammation, infection and tissue injury (Fig. 2, Table 1). The structures (Fig. 2) and nanogram actions of resolvins are extended to many pathologies including vascular [17], airway, dermal, renal, ocular, pain, cancer, fibrosis and wound healing [18]. This is also the case for neuroprotectins/protectins; each has actions throughout the body; *vide infra*.

Within self-limited exudates, RvD3 displays a unique timeframe compared to RvD1 and RvD2, appearing late in resolution, suggesting a key role of RvD3. RvD3's complete stereochemistry was recently established [11], and confirmed its potent anti-inflammatory and proresolving actions [4]. Macrophage biosynthesis of MaR1 and its potent proresolving and tissue regenerative actions (Fig. 2) are established [12], and involve a 13*S*,14*S*-epoxide-maresin intermediate that is also active and stimulates M1 to M2 phenotype-switch [12]. Also, both n-6 docosapentaenoic acid (DPA) and its n-3 form are substrates for SPM [19, 20]. Since n-3 DPA accumulates in certain individuals and is converted to potent n-3 immunoresolvents from each of the SPM families, it is likely n-3 DPA-derived SPM are compensatory in humans since they share resolvin and protectin actions [20].

Maresins are produced by macrophages from docosahexaenoic acid (DHA) and exert potent proresolving and tissue homeostatic actions. Maresin 1 (MaR1; 7R,14S-dihydroxy-docosa-4Z,8E,10E,12Z,16Z,19Z-hexaenoic acid) is the first identified maresin. Recently, we demonstrated formation, stereochemistry, and precursor role of 13,14-epoxy-docosahexaenoic acid, an intermediate in MaR1 biosynthesis. The 14-lipoxygenation of DHA by human macrophage 12-lipoxygenase (hm12-LOX) gave 14-hydro(peroxy)-docosahexaenoic acid (14-HpDHA), as well as several dihydroxy-docosahexaenoic acids, implicating an epoxide intermediate formation by this enzyme (see Table 2 and references within for the role of LOX and the SPM in mouse diseases). Using a stereo-controlled synthesis, enantiomerically pure 13S,14S-epoxy-docosa-4Z,7Z,9E,11E,16Z,19Z-hexaenoic acid (13S,14S-epoxy-DHA) was prepared, and its stereochemistry was confirmed by NMR spectroscopy. When this 13S,14S-epoxide was incubated with human macrophages, it was converted to MaR1. The synthetic 13S,14S-epoxide inhibited leukotriene B_4 (LTB_4) formation by human leukotriene A_4 hydrolase (LTA_4H) to a similar extent as LTA_4 but was not converted to MaR1 by this enzyme. 13S,14S-epoxy-DHA also reduced arachidonic acid conversion by hm12-LOX and promoted conversion of M1 macrophages to M2 phenotype, which produced more MaR1 from the epoxide than M1. Together, these findings establish the biosynthesis of the 13S,14S-epoxide, its absolute stereochemistry, its precursor role in MaR1 biosynthesis, and its own intrinsic bioactivity. Given its actions and role in MaR1 biosynthesis, this epoxide is now termed 13,14-epoxy-maresin (13,14-eMaR; Fig. 2, Panel C) and exhibits new mechanisms in resolution of inflammation in its ability to inhibit proinflammatory mediator production by LTA_4 hydrolase and to block arachidonate conversion by human 12-LOX rather than merely terminating phagocyte involvement.

Further, PCR mapping of 12-lipoxygenase (12-LOX) mRNA sequence in human macrophages and platelets showed that they are identical. This human 12-LOX mRNA and enzyme are expressed in monocyte-derived cell lineage, and enzyme expression levels increase with maturation to macrophages or dendritic cells. Recombinant human 12-LOX gave essentially equivalent catalytic efficiency (kcat/KM) with arachidonic acid (AA) and DHA as substrates. Lipid mediator metabololipidomics demonstrated that human macrophages produce a novel bioactive product 13,14-dihydroxy-docosahexaenoic acid in addition to MaR1. Co-incubations with human recombinant 12-LOX and soluble epoxide hydrolase (sEH) demonstrated that biosynthesis of 13,14-dihydroxy-docosahexaenoic acid (13,14-diHDHA) involves the 13S,14S-epoxy-maresin intermediate produced from DHA by 12-LOX, followed by conversion via soluble epoxide hydrolase (sEH) [21]. This new 13,14-diHDHA displayed potent anti-inflammatory and pro-resolving actions, and at 1 ng reduced neutrophil infiltration in mouse peritonitis by ~40% and at 10 pM enhanced human macrophage phagocytosis of zymosan by ~90%. However, MaR1 proved more potent than the 13R,14S-diHDHA at enhancing efferocytosis with human macrophages. Taken together, the present findings demonstrate that macrophages produced a novel bioactive product identified in the maresin metabolome as 13R,14S-dihydroxy-docosahexaenoic acid, from DHA via conversion by human 12-LOX followed by sEH. Given its potent bioactions, we coined 13R,14S-diHDHA maresin 2 (MaR2).

3. Aspirin vs. Nonsteroidal Anti-Inflammatory Drugs: Friends or Foes of Resolution?

PG are central to the vascular response, permitting diapedesis of PMN and monocytes to leave postcapillary venules, and their production via COX-1 and COX-2 is critical for initiation and timely resolution (Fig. 1) [22, 23]. PGE_2 and PGD_2 each evoke pro-inflammatory and anti-inflammatory responses that depend on location. PGE_2 enhances LTB_4-mediated PMN extravasation and tissue injury that is blocked, for example, by lipoxin A_4 (LXA_4) and its aspirin-triggered epimer 15-epi-LXA_4 [24], illustrating a pro-inflammatory PGE_2 function in skin and ability of 15-epi-LXA_4 stable analogs to stop PMN infiltration and tissue injury. Temporal LC-MS-MS-based profiling demonstrated the switch from PG and leukotriene production to appearance of lipoxins within inflammatory exudates (Fig. 1). PGE_2 or PGD_2 added to human PMN increase 15-LOX type I translation from mRNA stores in a cAMP-dependent manner, increasing LX biosynthesis [22].

Inhibition of COX-2 delays resolution [23] because prostaglandins play critical roles in resolution and are initiators of LM class switching (Fig. 1), a process involving utilization of omega-3 for resolvins and other SPM. In mapping resolution, it became clear that initiation of inflammation signals its end [15] and that leukocyte traffic in and out of pus permits prostanoids to signal biosynthesis of resolution mediators (Figure 1 & 2).

Disruption of physiologic LM class switching has deleterious consequences in mouse arthritis [25] and in humans [26]. To pinpoint, critical steps and mechanisms of SPM action within inflammation-resolution, we introduced quantitative indices [27] that are now widely used [28–30]. Resolution indices identified agents that disrupt or delay resolution (resolution interval, R_i), including COX-2 and lipoxygenase inhibitors [27, 28], lidocaine [31]. By

contrast, specific SPM, e.g. resolvins, lipoxins and protectins, shorten R_i by limiting PMN recruitment and stimulating macrophage efferocytosis (Fig. 1, Table 1) and bacterial killing [27, 29, 32, 33]; pinpointing the PMN-monocyte sequence needed for tissue repair and regeneration [12]; and glucocorticoids, specific cyclin-dependent kinase inhibitors, statins, annexin peptides and aspirin are resolution friendly [29, 34–36].

Aspirin and NSAIDs inhibit prostanoid biosynthesis, but aspirin is an irreversible inhibitor that acetylates COX, and NSAIDs are considered reversible inhibitors [2]. Aspirin acetylation of COX-2 modifies the catalytic domain, blocking PG-biosynthesis, which is well known, yet remains active producing 15*R*-HETE from arachidonic acid, 18*R*-HEPE from EPA and 17*R*-HDHA from DHA in cells carrying COX-2. These are transformed by leukocytes to aspirin-triggered lipoxins [35], aspirin-triggered resolvins [3, 4] and aspirin-triggered protectins [37]. Each AT-SPM is a potent mediator that stops PMN infiltration and enhances macrophage cleanup, giving a shortened R_i. COX-1 doesn't produce appreciable aspirin-triggered epimers. NSAIDs that inhibit both COX-1 and COX-2, and selective COX-2 inhibitors prevent their production [3].

Low-dose aspirin triggers 15-epi-LXA_4 in skin blisters in humans (75 mg aspirin daily/10 days) to reduce PMN infiltration [28]. In a randomized controlled study of 128 healthy volunteers, low-dose aspirin (8 weeks daily, 81 mg) increased plasma 15-epi-LXA_4. Low-dose aspirin thus enhances production of aspirin-triggering mediators in humans while inhibiting thromboxane, giving a net change [38] favorable for pro-resolution, where distinct resolution-phenotypes emerged [39, 40].

4. Microparticles and New Players in Local SPM Biosynthesis

Microparticles (MP) are membrane-derived vesicles produced by a range of cell types and contribute to human pathologies. MP from self-resolving exudates display anti-inflammatory and proresolving capacity [41]. Resolution-MP enhance efferocytosis [41, 42] and carry pro-resolving signals including hydroxy-SPM-precursors esterified in phospholipids [41]. Secretory PLA_2 ($sPLA_2$) releases these precursors from MP for conversion by leukocytes [41, 42]. Since nanomedicines are of wide interest [43], we used resolution-MP and their ability to shorten R_i in mouse peritonitis as a basis for biomimicry to construct humanized nanoparticles containing LXA_4 analog or AT-RvD1 [41]. These nano-proresolving medicines (NPRM) carrying SPM or SPM-analogs, enhance wound healing of human keratinocytes and are protective in a mouse model of temporomandibular joint disease [41]. There are currently limited treatments for TMJ diseases, and importantly NPRM display reduced nanotoxicity. Along these lines, NPRM containing a novel lipoxin analog (benzo-lipoxin A_4, $bLXA_4$) promote hard and soft tissue regeneration in periodontitis in the Hanford miniature pig. NPRM-$bLXA_4$ markedly reduces inflammatory cell infiltrate into chronic periodontal disease sites and increases new bone formation [44]. These findings offer a new therapeutic tissue-engineering approach for the treatment of chronic osteolytic inflammatory diseases.

New microfluidic chambers that permit visualization of cell-cell interactions between leukocyte subpopulations (i.e. human PMN and monocytes) and distinguish phlogistic vs.

nonphlogistic leukocyte behavior are ideal to screen SPM individually or incorporated within humanized NPRM [41, 45]. Single cell screening with microfluidic devices permits optimization for enriching MP with SPM and production of NPRM as well as viewing neutrophil-monocyte interactions [45] essential for appreciating signals used in the PMN-monocyte sequence (Figure 1).

Platelet-MP transfers its 12-LOX to mast cells for LX-biosynthesis [46] (see Figure 2, Panel B). Platelet-MP are taken up and enhance LXA_4 production, which reduces colitis in mice, suggesting that platelet-derived MP signal immune regulation via LXA_4 [46]. MP can also transfer substrate and intermediates to macrophages (MΦ) during efferocytosis enhancing SPM biosynthesis, demonstrated by transfer of deuterium label from precursors to labeled-SPM [42]. Myeloid cells at different stages display agonist- and phenotype-specific LM profiles. For example, human PMN from healthy peripheral blood produce predominantly LTB_4, while apoptotic PMN produce PGE_2, LXB_4 and RvE2 signals for resolution [42].

Both M1 and M2 macrophages display specific markers and pathways specialized to their functions of MΦ subpopulation in inflammation, its resolution and cancer [47]. Human M2 macrophages possess increased Arg1, 15-LOX [48], other markers and specific LM signature profiles. M2 produce SPM with lower LTB_4 and PG than M1. Both engulf apoptotic PMN, modulating their LM profiles. In M2, LTB_4 is down-regulated and SPM are increased [42], suggesting M1 and M2 subpopulation [47, 48] produce functional LM signatures that can impact both physiologic and pathophysiologic states [42]. Secreted PLA_2 group IID is a proresolving PLA_2 expressed in $CD11c^+$ dendritic cells and macrophages giving rise to RvD1 and PGJ_2 in lymphoid tissue, controlling hypersensitivity [49].

Eosinophils are well appreciated in parasitic infections and allergic responses. In severe asthma, PD1 is present in human exhaled breath condensates [30] and is decreased in human eosinophils from patients with severe asthma [50]. Human eosinophils are a major source of PD1, and at nanomolar concentrations, reduce adhesion molecules (CD11b and L-selectin), eotaxin-1/CCL11 and chemotaxis without affecting degranulation, superoxide generation or cell survival. Impaired PD1 in severe asthmatic patients may contribute to persistence and disease severity (Box 2). Eosinophils also stimulate resolution in mouse peritonitis via SPM initiated by mouse eosinophils [51]. LC-MS-MS-lipidomics identified LXA_4, RvD5, 17-HDHA and PD1 eosinophil production [51] and RvE3 (Fig. 2) that limit PMN infiltration and regulate MΦ [50, 52]. Hence, via their ability to produce SPM, eosinophils contribute to resolution. To support this, Arita and colleagues found eosinophil depletion leads to a deficit in resolution rescued by PD1 or eosinophil restoration. Thus, cellular traffic to inflammatory loci has a dynamic impact on LM signatures and specific SPM metabolomes activated within local milieu.

Box 2

General Points on Specialized Pro-resolving Mediators: What's Established

- **Mouse resolving exudates:** Temporal relationships and in vivo actions

  Air pouch, peritonitis, ischemia-reperfusion injury: sterile and bacterial infections

- **Structures of endogenous mediators elucidated:** Total organic synthesis

  Confirmation of potent actions and complete stereochemical assignments

- **Human cellular biosynthesis:**
  - apoptotic PMN, microparticles, Macrophages M1 and M2;
  - PMN-interactions with resident endothelial and epithelial cells; PMN-Platelets
- **Human Pathology – Present Yet Diminished SPM: Examples of failed resolution**

Asthma [163–165]	Localized aggressive periodontitis [166]
Adipose [167]	Multiple sclerosis patients [106]
Alzheimer's disease brain [89, 96]	Rheumatoid arthritis, synovial [168]
Breath condensates [30, 169]	Scleroderma [133]
Cystic fibrosis, nasal polys in cystic fibrosis [170]	Ulcerative colitis [171]

- **Conserved structures:** fish (trout, zebrafish, anchovy), mouse, rabbit, human
- **Tissue Regeneration: RvE1, MaR1**
- **Human Blood:** RvE1, RvE2 and 17*R/S*-HDHA, RvD1, RvD2 and 17-epi-RvD1
- **Human Milk; high levels of SPM:** LXA_4, RvD1, RvD2
- **Clinical development and human trials:** RvE1 mimetics

  Ocular indications; Phase III clinical trial

5. SPM Cellular Actions in Disease Models: Receptors and Resolution Mechanisms

SPM are now investigated in animal models of infection (Table 1 and Table 2 for disease models) by investigators worldwide (reviewed in [18]). These include airway, dermatologic, ocular, pain and organ-specific inflammation and tissue injury resulting from collateral damage from excess PMN [18]. The low SPM-doses required to stop ongoing inflammation and promote resolution rely on GPCR receptors via amplifying intracellular signals. Several SPM receptors are identified using library screening, labeled-ligands for specific binding (stereospecific nM K_d) and functional cellular responses. SPM in general do not utilize Ca^{2+} mobilization in leukocytes for signal transduction but rather activate phosphorylation demonstrated using genetically engineered mice (see Table 3). RvE1 specifically binds to ChemR23 [53] and BLT1 to evoke pro-resolving responses. RvE1 activation of ChemR23 enhances macrophage phagocytosis via phosphoprotein-mediated signaling [54]. RvE1 blocks LTB_4 binding and also signals via BLT1 to promote apoptosis of PMN for their clearance by MΦ [55] (LTB_4-BLT1 signals PMN survival). PMN RvE1 signaling involves blocking survival signals, an important difference for PMN in the innate response, where they must undergo timely apoptosis and MΦ efferocytosis to achieve homeostasis.

RvD1 binds and activates human GPR32 and shares human and murine LXA_4 receptor (ALX/FPR2) to evoke rapid impedance change with recombinant receptors. Transgenic mice overexpressing human ALX-FPR2 require less RvD1 to stop inflammation [56], and in receptor-deficient mice, RvD1 is apparently without leukocyte actions [57]. Resolution involves specific miR, regulated by SPM receptors [56, 58, 59]. RvD1-GPR32 upregulates miR-208 and IL-10 as well as miR-219, which decreases LTB_4 via regulation of 5-lipoxygenase [58].

miR regulation by SPM is an example of long-term SPM-receptor signaling. SPM receptors acutely signal as well. For example, recombinant RvD1-GPR32 blocks histamine receptor (H_1)-stimulated increases in intracellular Ca^{2+} in CHO cells via rapid stimulation of phosphorylation of H_1 receptor that stops Ca^{2+} mobilization [60]. This form of SPM signaling, first documented with conjunctival goblet cells and RvD1, is also functional in salivary glands [61], is likely to be relevant in human PMN, which rapidly stop and change shape on exposure to SPM [45].

In addition to RvD1 and LXA_4, ALX/FPR2 is also activated by peptide pro-resolving mediators, e.g. annexin A1, as well as pro-inflammatory peptides, at much higher concentrations [36]. This capacity of ALX/FPR2 involves ligand-biased receptor activation with heterodimerization of ALX with related FPR dictating pro-inflammatory signaling, and ALX homodimer gives pro-resolving signaling [36]. LXA_4 also enhances ALX/FPR2 promoter activity, which has a mutation of interest in human disease [62].

RvD3 and RvD5, related to RvD1 (Fig. 2), can also activate human GPR32 [11, 32]. Given the temporal production of these SPM in vivo (Fig. 2), these findings underscore that SPM produced locally at distinct times can impact different target cell types and receptors in a spatial-temporal dependency.

Both EPA and DHA activate GPR120 to signal responses of THP-1 cells [63], which are apparently not activated by resolvins. GPR120 is also a candidate taste receptor [64], requiring fatty acid (μM concentration) to evoke Ca^{2+} mobilization [65] that appears unrelated to SPM-resolution mechanisms, which are active at picomolar-nanomolar levels [42, 66].

6. Infectious Exudates and Resolution Programs in Host Defense

RvE1 and LXA_4 each reduce severity of periodontal disease in rabbits by enhancing *P. gingivalis* clearance, causative organism in this infection [67, 68]. While anti-inflammatory actions of SPM were established in sterile mouse models [3, 4], the relation between resolution and infection is of interest because of the known eventual immunosuppressive actions of anti-inflammatory drugs [69]. Surprisingly, RvD2 protects mice from cecal ligation-puncture (CLP)-induced sepsis [33], with potent actions enhancing phagocytosis and bacterial killing (Table 1, Box 1). In self-limited live *E. coli* infections, resolution programs are activated in mice and host PD1, RvD5 and RvD1 are elevated [32]. When added back to mouse phagocytes, human MΦ or PMN, SPM enhance bacterial phagocytosis and killing as well as clearance [32, 33, 70]. Of interest, SPM acting on the host lower antibiotic doses needed to clear infections.

LXA_4 is also protective in CLP in rats, reducing bacterial burden and pro-inflammatory mediators via a MΦ NFκB-mediated mechanism reducing systemic inflammation [71]. Aspirin-triggered-LXA_4 increases phagocytosis of *E. coli* in a PI3K-and scavenger receptor-dependent manner, and ALX/FPR2 is upregulated in patients with Crohn's disease and enhances bacterial clearance [72]. *Mycobacterium tuberculosis* infections also engage resolution programs via activating LTB_4-LXA_4 production, regulating host responses in zebrafish, mice and humans [73, 74]. Given importance of rising microbial resistance, activation of resolution programs and SPM-pathways could provide new anti-microbial approaches.

Herpes simplex virus causes ocular infections that lead to stromal keratitis with viral-initiated immunopathology. RvE1 and PD1 are each potent and topically active in this infectious mouse model, reducing pro-inflammatory mediators and stimulating IL-10 [75, 76]. H5N1 virus lethal dissemination activates genes in mice tracked to LX biosynthesis, where sustained inflammation inhibits LX-mediated anti-inflammatory host responses that permit viral dissemination [77]. H1N1 activates host resolution-metabolome increasing PD1 [78]. Host protectins display antiviral activity blocking replication of H5N1 influenza virus. During the time course of H3N2, a low-pathogenicity strain of influenza, anti-inflammatory mediators are produced with infection that correlates with resolution and SPM-related pathway-markers [79]. In children with acute post-streptococcal glomerulonephritis, resolution phase is associated with LXA_4 and diminished LTB_4 [80]. Pro-resolving actions of SPM also extend to yeast infections, e.g. *Candida*, where RvE1 enhances yeast killing and clearance [81]. Innate immunodeficiency syndromes are linked to mutations in innate receptors. For example, X-linked lymphoproliferative syndrome type-2 is associated with deficiency in X-linked inhibitor of apoptosis protein (XIAP). Mice deficient in XIAP are highly vulnerable in *Candida albicans* infection. RvD1 rescued Xiap(−/−) mice from lethal *C. albicans* infection, suggesting the potential therapeutic value of RvD1 in the treatment of innate immunodeficiency syndromes [82]. These results enforce the notion that treating the host during infection with host-directed pro-resolving molecules could open new opportunities in host-pathogen struggles [32, 70, 83].

7. Tissue Regeneration and Healing

LXA_4 stimulates reepithelialization of cornea in a gender-specific fashion [84]. RvE1, RvD1 and RvD2 each stimulate dermal wound healing, reducing neutrophilic infiltration and stimulate reepithelialization of skin wounds when applied to the wound site [85]. Most notably, they reduce the time required for dermal wound closure. D-series resolvins stimulate diabetic wound healing [86, 87].

Given the role of macrophages in wound healing and organ regeneration, the macrophage-derived SPM maresin pathway stimulates tissue regeneration. The maresin pathway and MaR1 (Figure 2) are also produced by planaria *Dugesia tigrina*, a Platyheminthes used in regeneration studies. RvE1 and MaR1 reduced regeneration time (speed of regrowing head segments). In the presence of inhibitor of MaR1 biosynthesis, regeneration index is reduced and rescued with addition of MaR1. Given the importance of tissue regeneration in trauma

and microbial invasion and infection, it is not surprising that SPMs play role(s) in stimulating organ regeneration [12].

8. Neuroinflammation, Pain, and Cognition

Resolvins and protectins are produced in mouse brain tissue [4, 88] and in human brain [89]. These include human microglial cells, where they reduce cytokine expression [4, 88] and their production by trout brain cells indicates SPM are conserved from fish to humans [90]. In mouse ischemic stroke, resolvins, protectins and their aspirin-triggered forms are produced [91], where they are protective, down regulating excess leukocyte infiltration, and reduce local neuronal injury, COX-2 induction, IL-1β and NFκB. Thus, in brain, DHA is precursor to neuroprotective signaling pathways evoked by ischemia-reflow tissue injury. Given its potent actions to reduce neuroinflammation and protect neural cells, we coined this 10,17-dihydroxy-protectin (a docosatriene) *neuroprotectin D1* with Bazan and colleagues when biosynthesized and acting in neural tissues and retinal epithelial cells [92].

DHA is enriched in brain, synapses and retina, where its protective role is appreciated, yet its role as a precursor to novel local mediators in resolution and in neuroprotection is still emerging. Bazan and colleagues showed potent protective roles of NPD1 in the nervous system, reducing stress pathways that lead to cell death and increase cell survival, and in several ocular models of important diseases NPD1 targets microglia [4, 93]. Aspirin-triggered DHA metabolome biosynthesizes 17*R*-NPD1/PD1 that reduces human PMN transmigration, and enhanced MΦ efferocytosis [37] and attenuates cerebral ischemic injury [94]. AT-NPD1 reduces brain edema in the penumbra and subcortical lesion size, infarct volumes are reduced ~60–80%, and improves neurological scores [94]. Hence, new findings focus on unesterified DHA in neural tissues as an important determinant in brain SPM biosynthesis and neuroinflammation [95].

In human Alzheimer's disease (AD), brain NPD1 is reduced [89], implicating that its loss contributes to neurodegeneration. Indeed, resolution-pathway (SPM-receptors and products) are diminished in brain from AD [96]. LXA_4 and RvD1 are reduced in cerebrospinal fluid and hippocampus that correlated to mini-mental state examinations in these patients, which together provide further evidence that failed resolution mechanisms may contribute to human disease and cognitive function [96]. RvD1 added to leukocyte-derived MΦ from AD patients reduces their pro-inflammatory phenotype and enhances their ability to promote phagocytosis of amyloid-beta (Aβ) [97], suggesting that resolvins promote clearance of Aβ deposition to reduce inflammation in AD. Human MΦ from patients with amyotrophic lateral sclerosis, a neuronal degenerative disease, demonstrates that RvD1 reduces their output of pro-inflammatory cytokines and chemokines that contribute to neuroinflammation [98]. RvD1 reduces IL-6 and TNFα by ALS-MΦ and is ~1,000 times more potent than DHA [98]. Hence, resolvins are protective and are likely to play pivotal roles in homeostasis in brain and peripheral tissues, each with selective functions that can impact neuroinflammation, its resolution and cognitive function.

Given the potent actions of resolvins and protectins in neuroinflammation, several groups investigated LX in neurologic systems. LXA_4 also displays potent neuroprotection, reducing

PMN infiltration, astrocyte activation, TNFα and IL-1β in a rat model of cerebral artery occlusion and ischemia [99], reduces β-amyloid-induced IL-1β and TNFα in cortex and hippocampus of mice [100], is neuroprotective in cerebral ischemia-reperfusion injury in rats [101, 102] and reduces leukotrienes as well as ERK phosphorylation, which limits local neuroinflammation partly mediated by ALX/FPR2 [101]. In experimental stroke, PPAR agonist rosiglitazone is neuroprotective via increasing LXA_4 and reducing leukotriene B_4 [103]. In rat cerebral ischemia/reperfusion, LXA_4 reduces infarct size and improves neurologic scores that are only partially attributed to receptor ALX/FPR2, and induces Nrf2 expression and nuclear translocation as well as heme oxygenase HO-1 [104], suggesting that both receptor-mediated pathways and Nrf2 expression contribute to neuroprotection. LXA_4 is produced in brain and is protective via CB1 cannabinoid receptor [105] as an endogenous allosteric enhancer. LXA_4 enhances affinity of anandamide, potentiates endocannabinoids and protects from spatial memory loss induced by β-amyloid peptide [105, 106].

Inflammation can evoke pain that may persist, and each SPM displays targeted actions that resolve pain signals. Lipoxins reduce pain in murine models, LXA_4 receptor (ALX/FPR2) is on spinal astrocytes, and local spinal LXA_4, LXB_4 or their metabolically stable analogs reduces inflammation-induced pain [107]. LXs reduce thermal hyperalgesia with as little as 10 μg/kg given i.v. or 0.3 nmol (1 μL/h, 20–24 h) intrathecal (i.t.) [107]. Each SPM dampens pain, having specific targets of action [108] first demonstrated with RvE1 and RvD1 for inflammatory pain involving both central and peripheral sites of action [109]. RvE1 administered *i.t.* in mice is more potent than morphine or COX-2 inhibitor. RvE1 receptor (ChemR23) is in DRG, where RvE1 regulates pERK-dependent TRPV1inhibition and TNFα-mediated hyperalgesia centrally, and in postsynaptic neurons RvE1 inhibits glutamate and TNFα stimulation of NMDA-R and mechanical allodynia [109].

RvD1 inhibits TRPA1, TRPV3 and TRPV4 channel activation expressed in HEK cells in nanomolar-micromolar range, cultured sensory neurons and keratinocytes as well as displays analgesic properties in pain behavior [110]. AT-RvD1 appears specific for TRPV3 [111], and NPD1/PD1 (0.1–10 ng) blocks spinal LTP, reducing TRPV1-dependent inflammatory pain without affecting basal pain responses [112]. NPD1 also reduces TNFα-dependent pain hypersensitivity [112] and protects against neuropathic pain after nerve trauma in mice [113]. RvD2 inhibits TRPV1 (IC_{50} 0.1 nM) and TRPA1 (IC_{50} 2 nM) in primary sensory neurons. RvE1 selectively blocks TRPV1 (EC_{50} = 1 nM), and RvD1 inhibits TRPA1 (IC_{50} 9 nM). RvD2, RvE1 and RvD1 (Fig. 2) each differentially regulate TRPV1 and TRPA1 agonist-elicited acute pain and synaptic plasticity in spinal cord [114].

MaR1 inhibits TRPV1 currents in neurons and blocks capsaicin-induced inward current (IC_{50} 0.49 nM), diminishing inflammatory and chemotherapy-evoked neuropathic pain in mice [12]. RvD1 reduces postoperative pain [115], and both AT-RvD1 and 17*R*-HDHA reduce adjuvant-induced arthritis in rats and associated pain [116], reducing NFκB and COX-2 expression in spinal cord, and within arthritic joints reduce TNFα and IL-1β. In addition to leukocytes and microglia, the currently known SPM-GPC receptors are present on neuronal bodies (DRG), nerve terminals (skin and muscle) and synaptic terminals, where they regulate specific TRP channels. For example, RvE1-ChemR23 (ERV) interaction in DRG regulates TRPV1, but not via direct activation of channels like endocannabinoids

[108] or other lipids that act to directly bind TRP channels in micromolar range; rather each SPM activates specific GPCR in pico-nanomolar range to regulate TRP channels involved in pain signaling.

Direct comparisons between LXA_4 and AT-RvD1 in rat mechanical hypersensitivity in inflammation-induced pain indicate that both effectively reduce hypersensitivity and pro-inflammatory mediators from astrocytes [117]. Cognitive decline following major surgery or critical illness is a major public health concern. Cognitive decline results from local increases in pro-inflammatory mediators. Systemic AT-RvD1 prophylaxis improves memory decline in a mouse surgery model and protects from postoperative neuronal dysfunction. AT-RvD1 reduces IL-6 and stimulated endogenous LXA_4 [118], implicating positive feed-forward mechanisms in resolution. A human randomized trial of n-3 PUFA dietary intervention in chronic headache found increasing n-3 PUFA associated with reduced headache-pain and increased RvD2, 17-HDHA and 18-HEPE (pro-resolving pathway markers) [119] suggesting local SPM may reduce headache pain in humans as in animal models of pain and behavior.

9. Cross-talk between SPM and nervous systems

In zymosan-initiated acute peritoneal inflammation, vagus nerve regulates local expression of netrin-1, an axonal guidance molecule that activates resolution. Vagotomy reduces local SPM and delays resolution. In netrin-1(+/−) mice, resolvin D1 (RvD1) was less effective in promoting resolution of peritonitis compared with Ntn1(+/+). Netrin-1 and RvD1 display bidirectional activation in that they stimulated each other's expression and enhanced efferocytosis [120]. These results indicate that the vagus nerve regulates both netrin-1 and SPM, which act in a bidirectional fashion to stimulate resolution, providing evidence for local neuronal control of resolution.

It was reported recently that in the mouse fibromyalgia-like model induced by reserpine, administration of AT-RvD1 and RvD2 significantly reduced mechanical allodynia, thermal sensitization and prevented the depressive-like behavior in reserpine-treated animals. Reserpine triggers a marked decrease of dopamine and serotonin (5-HT) levels. Long-term treatment with RvD2 prevents loss of serotonin in total brain, and AT-RvD1 leads to recovery of dopamine levels in cortex [121]. Therefore, D-series resolvins reduce painful and depressive symptoms associated with fibromyalgia in mice.

10. Reproductive System

In pregnant women, LXA_4 is found in circulation at 24 weeks gestation and in lower levels in non-pregnant women [122–124]. Myometrial biopsies from pregnant women show ALX/FPR2 present on myocytes and neutrophils with LXA_4 reducing agonist-stimulated IL-6 and IL-8 in myometrium, which suggesting LX may stimulate resolution of local inflammation in both physiologic and pathologic labor in human parturition [122]. LXA_4 also modulates estrogen receptor [125] and blocks embryo implantation [126]. In patients and in rat endometrium with ectopic endometriosis, ALX/FPR2 showed higher expression [127]. Since SPM like LXA_4 counter-regulate pro-inflammatory cytokines (Box I), LXA_4 reverses LPS-induced miscarriages down regulating both uterine and pro-inflammatory mediators

from placenta and mast cells in this tissue [123], and may be useful in endometriosis-related infertility [128]. During stress, the mechanism involves inactivation of glucocorticoids inhibiting LX-biosynthesis [123] controlling local inflammatory-homeostasis in pregnancy, suggesting a physiologic role for SPM (Fig. 3A).

In preeclampsia, LX counters pro-inflammatory factors produced in women that stimulate PMN adhesion to vascular endothelial cells [129], and LX appear to regulate implantation which may be useful in contraception. Certainly enzymes that produce SPM are in rat placental tissue and are regulated during gestation [130]. RvE3 in pregnant mice lowers local inflammatory milieu and incidence of preterm birth [131]. D-series resolvins RvD1, RvD2 and protectins (PD1 and 10S,17S-diHDHA, a.k.a. PDx; Cayman Chemical) are present in placenta and are increased with dietary omega-3 [130]. Another strategic location for SPM is in human breast milk [132], where they are orders of magnitude higher levels than inflammatory sites. LXA_4, RvD1 and RvE1, identified in milk from mothers during the first month of lactation [132], may each have role(s) in neonatal immunity.

11. Organ Fibrosis

Unresolved inflammation, epithelial and microvascular injury can lead to excessive fibrosis that impairs organ function. In many organs such as lung and kidney, the cause is unknown and can lead to morbidity. Leukotrienes are profibrotic and in humans with scleroderma interstitial lung disease, the relationship between leukotrienes and lipoxins is imbalanced, with LXA_4 in bronchoalveolar lavages at levels unable to counter-regulate profibrotic factors [133]. Aspirin-triggered-LX analog reduces bleomycin-induced pulmonary fibrosis [134], and both LXA_4 and benzo-LXA_4 reduce renal fibrosis [135]. RvE1 and RvD1 protect from renal fibrosis by reducing collagen I and IV, α-SMA and fibronectin [136]. Also, RvD1 reduces pro-inflammatory mediators generated by cigarette smoke exposure and pulmonary toxicants [137] that may reduce COPD-like fibrosis.

12. Cancer Resolution

Unresolved inflammation may link to predisposition to carcinogenesis and tumor invasiveness [3, 138]. RvD1 is chemopreventive in colitis-associated colon carcinogenesis in mice [139, 140]. With D. Panigrahy and colleagues, we found both RvD1 and RvD2 reduce tumor growth in mice in nanogram amounts [141] and may be useful together with cancer chemotherapies.

13. SPM link Innate to Adaptive Immunity

Lymphoid tissue, e.g. mouse spleen, produces RvD1, 17-HDHA, PD1 [142] and LXA_4 [143] from endogenous sources, suggesting they’re strategically positioned to act on lymphocytes (Fig. 1). Both 17-HDHA and RvD1 increase human B cell IgM and IgG, a response not shared by PD1. 17-HDHA augments B cell differentiation toward CD27(+)CD38(+) antibody-secreting cell phenotype [142]. PD1 is biosynthesized by human T helper 2-skewed mononuclear cells via 16(17)-epoxy-protectin intermediate (Figs. 2 and 3) and reduces T cell migration, TNFα and INFγ while promoting T cell apoptosis [144]. LXA_4, RvE1 and PD1 each upregulate CCR5 expression on leukocytes that bind

chemokines, facilitating their clearance and resolution [145]. PD1 reduces $CD4^+$ T cell infiltration into cornea [75], as does RvE1 in *Herpes simplex* viral infections [76]. RvD1 reduces $CD11b^+$ leukocytes and $CD4^+$ and $CD8^+$ T lymphocytes within the eye in uveitis [146]. RvE1 and RvD1 each regulate T-cell activation in choroid-retina [147]. RvE1 induces apoptosis of activated T cells via 2,3-dioxygenase induction in DC giving a new functional DC-subtype in resolution [148]. RvE1 reduces mouse $CD4^+$ T cells and $CD8^+$ T cells in atopic dermatitis [149].

14. Additional n-3 Pathways and Products

Identification of novel n-3 mediators and ability to profile using LC-MS-MS-based lipidomics [3, 4] opened the possibility for additional pathways that can convert n-3 to bioactive molecules. Recently, Hammock and colleagues found cytochrome P450 epoxygenases convert DHA (Fig. 3B) to EET-like structures that inhibit VEGF and fibroblast growth factor 2-induced angiogenesis. When epoxydocosapentaenoic acids are given to mice with soluble epoxide hydrolase inhibitor, they are blocked from further metabolism, reducing ~70 tumor growth and metastasis [150]. Epoxyeicosatrienoic acids (EETs) evoke an opposite action in micromolar range, increasing tumor progression and angiogenesis [150]. These opposing actions are intriguing, because both the n-3 and n-6 epoxy-products are present in healthy subjects with n-3 supplementation, that display a high degree of inter-individual variability in metabolite phenotyping of these pathways (Fig 3 B) using lipidomics [151].

In addition to epoxidation, p450 monooxygenases can convert PUFA to hydroxy-containing products similar to lipoxygenases, but via a different mechanism [152]. Some of these hydroxy p450-products (i.e. 17-HDHA) are converted in vivo to D-series resolvins [152]. EPA is substrate for prostanoid-like products, some of which exert potent actions; e.g., Δ12-PGJ_3 targets leukemia stem cells, activating apoptosis via Michael adducts [153] (Fig. 3B). Human leukocytes can also convert hydroxy-n-3 PUFA to electrophilic α,β unsaturated ketone derivatives that activate Nrf2-dependent gene expression and suppress NF-κB pro-inflammatory-gene expression [154]. Oxidative stress promotes DHA conversion to neuroisoprostanes [155] as well as oxidized phospholipid derivatives that resolve neuroinflammation, uncovered using functional lipidomics [156] active in experimental autoimmune encephalomyelitis and brain lesions in multiple sclerosis.

15. Human studies

Since resolvins and protectins were first identified in mouse exudates, it was essential to establish their biosynthesis by human leukocytes and in human tissues [3, 4, 88]. RvE1 and RvE2 are produced in human blood [53, 70, 157], providing substrate is available. RvD1 and RvD2 are also present in human blood at concentrations commensurate with their known bioactivities [158], and in human milk [132], identifications made possible with LC-MS-MS and availability of SPM [16], thus opening the opportunity for rigorous assessment of their functional roles and potential in human physiology (Table 4, human SPM production).

Muscle inflammation; resistance exercise—In an elegant study, Markworth et al. [26] demonstrated lipid mediator class switching in humans. Using a strenuous resistance exercise protocol, venous blood was collected during the time course post exercise and lipid mediators present in peripheral blood were identified using LC-MS-MS-lipidomics. Initial post-exercise recovery phase demonstrated the presence of prostanoids followed by leukotrienes, EETs and p450-derived eicosanoids, as well as LX, resolvins and protectins. Widely used NSAID for muscle aches and pains, ibuprofen, blocks exercise-induced prostanoids as well as reduces LTB_4 and delays and diminishes the appearance of SPM. Resistance-exercise in humans illustrates the initial acute pro-inflammatory mediators and their link to resolution programs [26].

Lipoxin analogs were designed that are topically active [24], orally active, and efficacious in mouse and guinea pig skin inflammation, reducing edema, PMN and eosinophil infiltration and epidermal hyperproliferation [159] in preclinical models that could provide an alternative to using corticosteroids in certain settings. ATL analog is more potent than LTB_4 receptor antagonist or glucocorticoid [159]. One setting is pediatric use of steroids. In infantile eczema, topical 15(*R/S*)-methyl-LXA_4 relieved severity and improved quality of life without apparent adverse events in a double-blind trial [160]. In these infants, AT-LXA_4 analog was as effective as a steroid mometasone. Also, inhaled LXA_4 is safe and efficacious with asthmatic adults [161].

15.1. SPM resolution agonists in clinical development

RvE1, MaR1 and NPD1/PD1 are each in clinical development programs licensed by Brigham and Women's Hospital/Partners Health Care. RvE1 mimetic is in development for ocular indications[1], and NPD1/PD1 for neurodegenerative diseases and hearing loss[2], given their broad ability to regulate inflammation without immunosuppression. Results from their pharmacology in animals [18] suggest treatment of inflammation-associated disease may be possible with SPM-agonists, which can reduce the use of inhibitors or antagonists that eventually can turn immunosuppressive [69].

16. New Pathway in Tissue Regeneration and Host Defense

Upon infection and inflammation, tissue repair and regeneration are essential in reestablishing function. We identified potent molecules present in self-limited infectious murine exudates, regenerating planaria, human milk as well as macrophages that stimulated tissue regeneration in planaria and are pro-resolving [162]. Characterization of their physical properties and isotope tracking indicated that the bioactive structures contained docosahexaenoic acid and sulfido-conjugated (SC) triene double bonds that proved to be 13-glutathionyl,14-hydroxy-docosahexaenoic acid (SCI) and 13-cysteinylglycinyl, 14-hydroxy-docosahexaenoic acid (SCII). These molecules rescued *E. coli* infection-mediated delay in tissue regeneration in planaria, improving regeneration intervals from ~4.2 to ~3.7 days. Administration of SC protected mice from second organ reflow injury, promoting repair via limiting neutrophil infiltration, upregulating Ki67 and Roof plate-specific spondin 3. At

[1]Auven Therapeutics. RX 10045 – ocular inflammation. http://www.auventx.com/auven/products/rx10045.php
[2]Anida Pharma Inc. Neuroprotectin D1. http://www.anidapharma.com/lead-molecule.html

nanomolar potencies these conjugates also resolved *E. coli* infections by limiting neutrophil infiltration, stimulating bacteria phagocytosis and clearance as well as efferocytosis of apoptotic cells. Together, these findings identify previously undescribed, conserved chemical signals and pathways in planaria, mice and human tissues that enhance host responses to contain infections, stimulate resolution of inflammation and promote the restoration of function.

17. Summation

Heat, redness, swelling, pain and loss of function are the cardinal signs of inflammation, each evoked by mediators, and an emerging body of evidence indicates that they are physiologically counterregulated by SPM. It's when and where that counts for autacoids, and it's important to emphasize that the first response of acute inflammation is ubiquitous and mounts throughout the body. Both n-6 and n-3 PUFA play critical and distinct roles in SPM biosynthesis of local mediators that are agonists; namely, immunoresolvents stimulating resolution by cessation of PMN influx and enhancing phagocytosis for clearance and containment, the hallmarks of resolution (Fig. 1). These are the defining SPM functions, with each SPM possessing additional nonredundant roles (Fig. 3) and more likely to be uncovered. At the cellular and molecular level, SPM counterregulate pro-inflammatory chemokines, cytokines and regulate adipokines; regulate miR, transcription and translocation, cell traffic and enhance microbial killing via GPCR-mediated mechanisms (Table 1). SPM are produced in humans (blood, milk and brain) where they can have physiologic actions because they are produced in levels that display potent selective actions in animals [17, 18]. SPM location within lymphoid tissues and actions with lymphocytes place them in strategic positions for communications from innate to adaptive immunity.

These exciting new findings from laboratories worldwide raise many questions on, e.g., whether SPM along with their local actions are also capable of evoking responses at sites distant from their origins. Ample n-3 and n-6 levels in humans are needed to biosynthesize PUFA-derived signals for the inflammatory response that evolved to protect the host. What are optimal levels of n-3 and n-6 PUFA needed to ensure local SPM-biosynthesis and eicosanoids required for timely resolution and homeostasis? Are there age- and gender-related components in SPM-resolution programs? Can we personalize nutrition to optimize local SPM production using LM-metabolipidomic profiling? Is it possible to design therapeutic diets to increase SPM [119], related products [150], and/or use select SPM-receptor agonists to control diseases? Is there a negative side to prolonged supraphysiologic SPM or related n-3-PUFA-derived products? The immediate future will bring evidence to address these fundamental questions now that the SPM structure and spatial temporal resolution-metabolomes are under intensive investigations.

SPM and new PUFA products (Fig. 5) emerge as key regulators in physiologic pathways in unresolved inflammation, obesity, cognitive decline, reproduction, neuroprotection and cancer, beyond PUFA roles in intermediary metabolism and membrane physical dynamics. Identification of SPM metabolomes and the appreciation that exudates drive resolution in part via SPM proresolving actions has set a new terrain in physiology. Moreover, SPM are now proven to have a wide range of actions that open a new vista for resolution physiology

and pharmacology, where the mediators and their precursors are vital in supplying chemical signals for catabasis to homeostasis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

17R-HDHA	17*R*-hydroxy-4Z,7Z,10Z,13Z,15E,19Z-docosahexaenoic acid
AT	aspirin-triggered
AT-RvD3	4*S*,11*R*,17*R*-trihydroxydocosa-5*Z*,7*E*,9*E*,13*Z*,15*E*,19*Z*-hexaenoic acid
GPCR	G protein-coupled receptor
LC-MS-MS	liquid chromatography-tandem mass spectrometry
LM	lipid mediator
LT	leukotriene
LTB_4	leukotriene B_4, 5*S*,12*R*-dihydroxy-6*Z*,8*E*,10*E*,14*Z*-eicosatetraenoic acid
LXA_4	lipoxin A_4, 5*S*,6*R*,15*S*-trihydroxy-7*E*,9*E*,11*Z*,13*E*-eicosatetraenoic acid
LXB_4	lipoxin B_4, 5*S*,14*R*,15*S*-trihydroxy-6*E*,8*Z*,10*E*,12*E*-eicosatetraenoic acid
MaR1	maresin 1, 7*R*,14*S*-dihydroxy-docosa-4*Z*,8*E*,10*E*,12*Z*,16*Z*,19*Z*-hexaenoic acid
MΦ	macrophages
PD1/NPD1	protectin D1/neuroprotectin D1, 10*R*,17*S*-dihydroxy-4*Z*,7*Z*,11*E*,13*E*,15*Z*, 19*Z*-docosahexaenoic acid
PMN	polymorphonuclear neutrophil
PG	prostaglandin
PGE_2	Prostaglandin E_2, 9-oxo-11*R*,15*S*-dihydroxy-5*Z*,13*E*-prostadienoic acid
PUFA	polyunsaturated fatty acid
Rv	resolvin
RvD1	resolvin D1, 7*S*, 8*R*,17*S*-trihydroxy-4*Z*, 9*E*, 11*E*, 13*Z*, 15*E*, 19*Z*-docosahexaenoic acid)
RvD2	resolvin D2, 7*S*, 16*R*, 17*S*-trihydroxy-4*Z*, 8*E*, 10*Z*, 12*E*, 14*E*,19*Z*-docosahexaenoic acid

RvD3	resolvin D3, 4*S*,11*R*,17*S*-trihydroxydocosa-5*Z*,7*E*,9*E*,13*Z*,15*E*,19*Z*-hexaenoic acid
RvD5	Resolvin D5, 7*S*,17*S*-dihydroxy-4*Z*,8*E*,10*Z*,13*Z*,15*E*,19*Z*-docosahexaenoic acid
RvE1	resolvin E1, 5*S*,12*R*,18*R*-trihydroxy-6*Z*,8*E*,10*E*,14*Z*,16*E*-eicosapentaenoic acid
RvE2	resolvin E2, 5*S*,18*R*-trihydroxy-6*E*,8*Z*,11*Z*,14*Z*,16*E*-eicosapentaenoic acid
SPM	specialized pro-resolving mediators
TRP	transient receptor potential

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Highlights

- Biosynthesis of specialized proresolving mediators (SPM)
- Functions of resolvins, lipoxins, protectins and maresins
- SPM actions in animal models of disease

Figure 1A

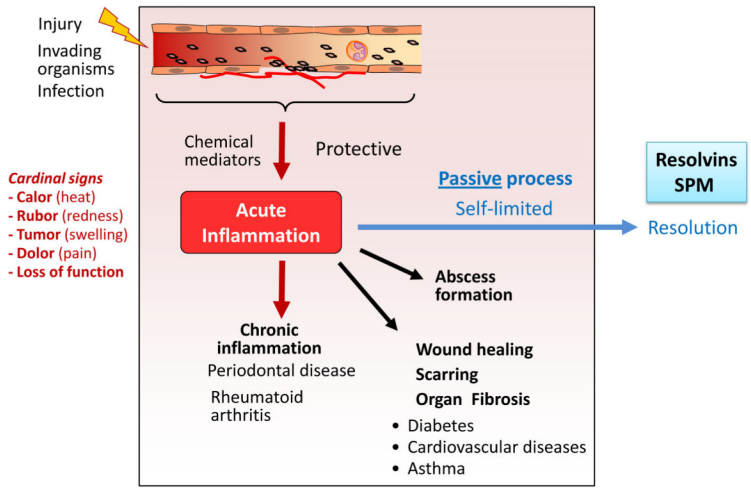
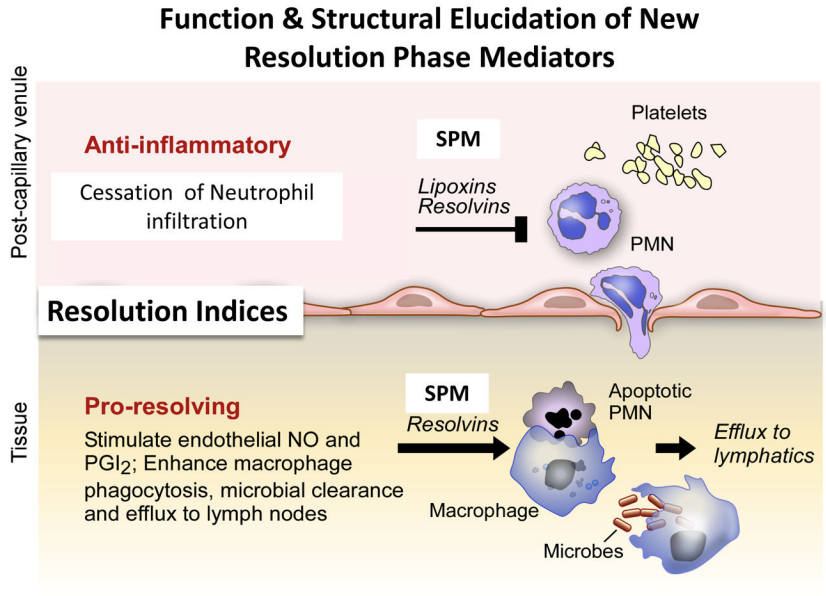


Figure 1 panel A

Figure 1B



Main Cellular Responses and role of SPM in Resolution of Inflammation

Figure 1 panel B

Figure 1. Lipid mediators in the acute inflammatory response and its outcomes

Panel A: LM play pivotal roles in the vascular response and leukocyte trafficking, from initiation to resolution. Eicosanoids are critical in initiating the cardinal signs of inflammation, and the specialized proresolving mediators (SPM), illustrated above, play key roles stimulating resolution (*Panel B*). Depicted are some roles of resolvins, protectins and maresins, SPM, in leukocyte trafficking, lipid mediator class switching, efferocytosis, resolving exudates to homeostasis and signaling to adaptive immunity via lymphocytes.

Failed resolution can lead to enhanced prostaglandin and leukotriene production and chronic inflammation that can lead to fibrosis. SPM (lipoxins, resolvins, protectins and maresins) counterregulate pro-inflammatory chemical mediators, reducing inflammation, and stimulate reepithelialization, wound healing, and tissue regeneration (see text for details).

Figure 2A

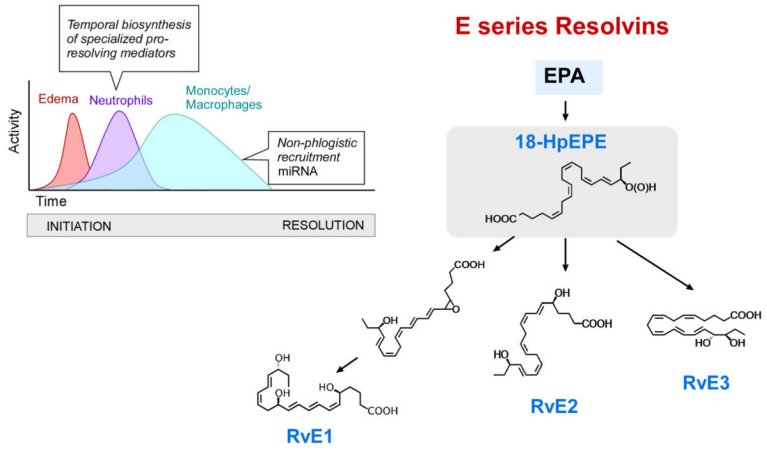


Figure 2 panel A

Figure 2B

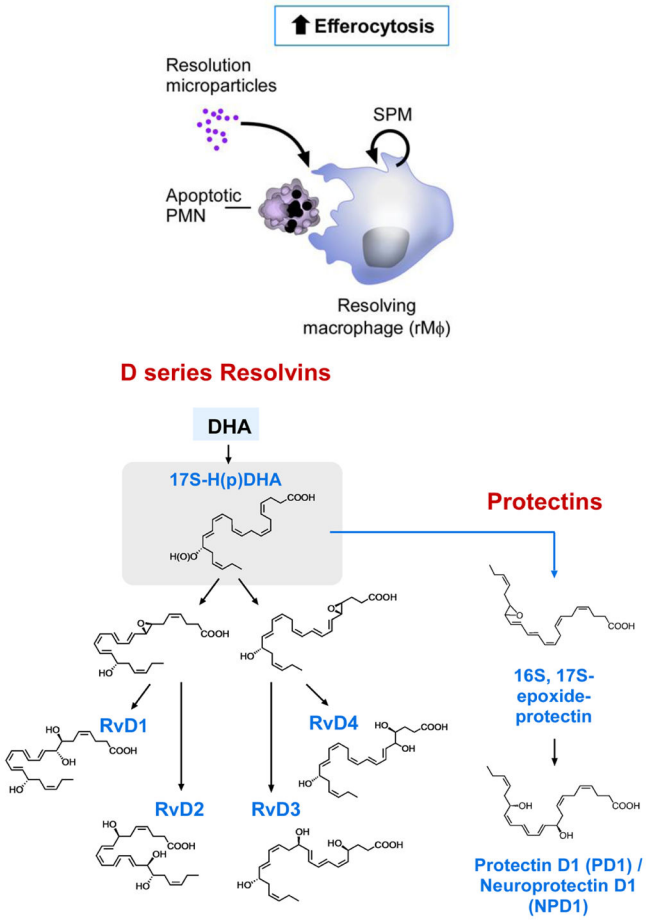


Figure 2 panel B

Figure 2C

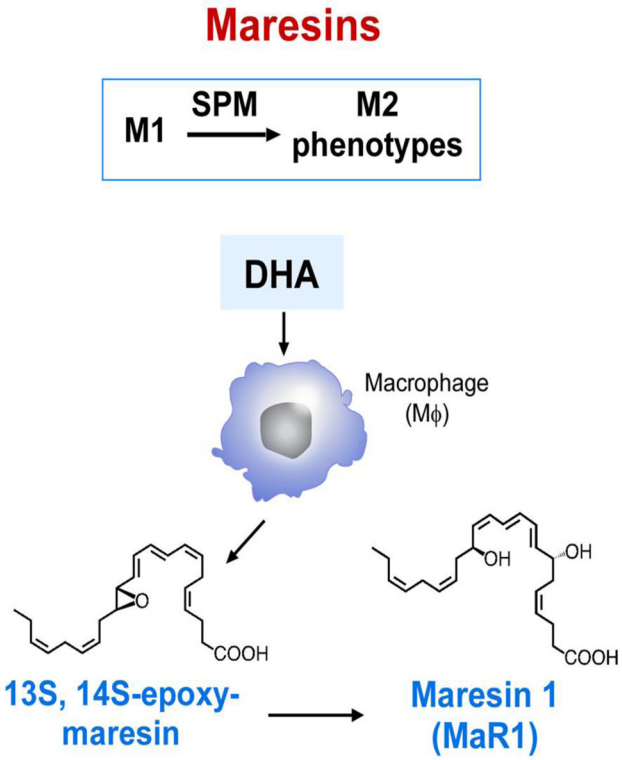


Figure 2 panel C

Figure 2. Production of SPM by resolving inflammatory exudates

Panel A depicts pus formation, e.g. a purulent exudate beginning with the postcapillary venule and the diapedesis of neutrophils as they are summoned by chemoattractants to leave the vascular circulation to combat invading microbes or foreign objects. The endothelial cell interactions with PMN are a site for E-series resolvin biosynthesis (see text for details). *Panel B* depicts the time course of self-limited acute inflammatory response, edema, followed by neutrophilic infiltration and nonphlogistic recruitment of monocytes/ macrophages from initiation (time 0) to resolution and the uptake of apoptotic PMN by resolving macrophages (rMΦ). Initial biosynthesis of SPM occurs at maximal neutrophilic infiltration through resolution in self-limiting responses. Structures of SPM: D-series resolvins, protectins and *(Panel C)* maresins. Depicted are resolvins D1–D4, which carry potent actions. 17-HpDHA is also precursor to 16,17-epoxide-protectin intermediate that is converted to protectin D1/neuroprotectin D1 and related protectins such as PDx, 10*S*,17*S*-diHDHA. *Panel C:* Maresins are produced by macrophages via initial lipoxygenation at carbon-14 position by lipoxygenation and insertion of molecular oxygen, producing a 13*S*, 14*S*-epoxide-maresin intermediate that is enzymatically converted to maresin-1. The

stereochemistry of each bioactive SPM is established, and SPM biosynthesis in murine exudates and human tissues confirmed. See ref. [16] for citations of original reports, total organic synthesis and stereochemical assignments and the text for further details.

Figure 3A

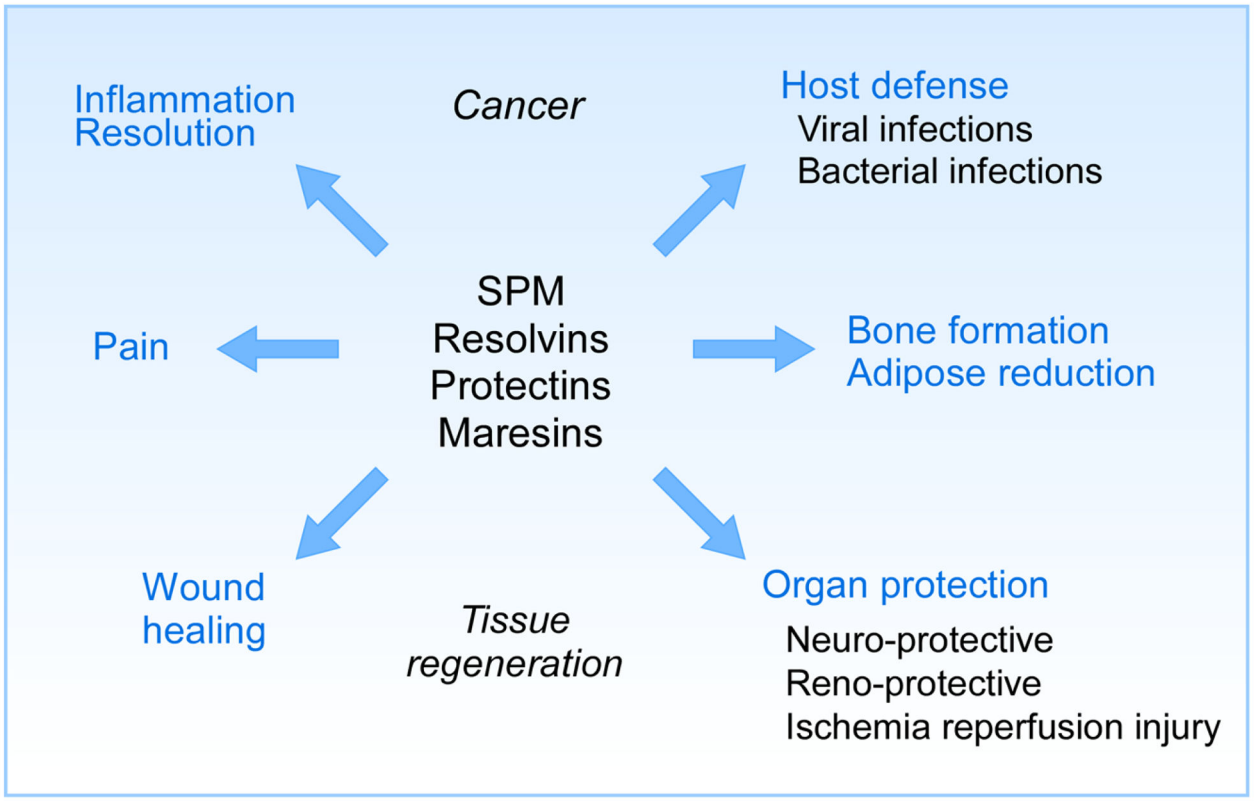


Figure 3 panel A

Figure 3B

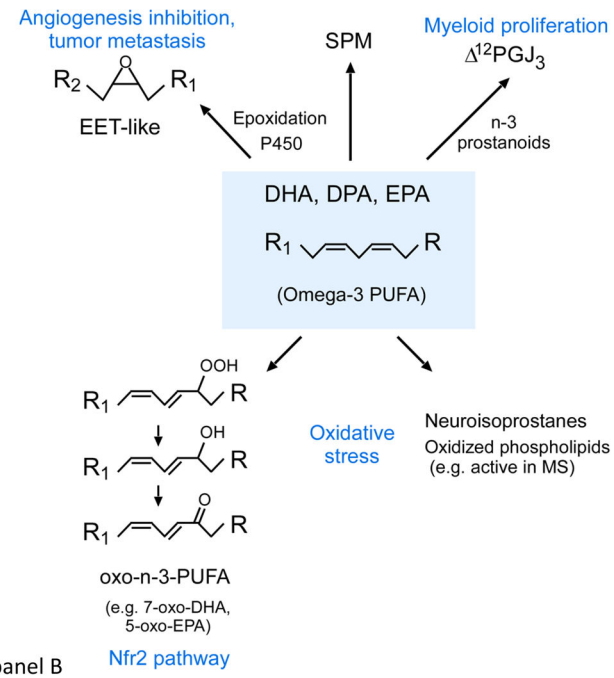


Figure 3 panel B

Figure 3. New lipid mediators and biosynthesis routes

Panel A: SPM actions. *Panel B:* New routes for n-3 essential fatty acids (DHA, DPA and EPA) conversion via P450 cyclooxygenase, lipoxygenase and oxidative pathways.

Table 1

SPM Shorten Resolution of Infections, Increase Survival and Outcomes in Murine Infection and Disease Models

SPM	Increase Survival	Disease	Shorten Resolution	Reference
LXA_4	+	Bacterial infections		Walker et al. [71]
15-epi- LXA_4	+	Lung injury		El Kebir et al. [172]
RvE1	+	Colitis	+	Arita et al. [173]
	+	*Candida* yeast	+	Haas-Stapleton et al. [81]
	+	Acid-induced lung injury	+	Levy and Serhan [30]
RvD1, RvD5, PD1	+	*E. coli* infection	+	Chiang et al. [32]
RvD1	+	Acute lung injury	+	Wang et al. [174]
RvD2	+	Cecal ligation and puncture sepsis	+	Spite et al. [33]
	+	Burn wound	+	Bohr et al. [175]

Table 2

Anti-inflammatory and tissue-protective roles: 12/15-LOX, 5-LOX and their products

(A) 12/15-LOX			
Animal models	**Alox15 gene modification**	**Actions/Phenotypes**	**References**
Periodontitis in rabbit	Alox15 transgenic	↓ PMN-mediated tissue degradation and bone loss	[67]
Cornea injury	Alox12/15 deficient mice	↑ Inflammation ↓ Wound healing ↓ Corneal re-epithelialization ↓ Endogenous LXA_4 production ↓ Heme-oxygenase 1 ***LXA_4 rescues exacerbated inflammation and impaired wound healing in Alox15 deficient mice***	[176, 177]
Atherosclerosis	Alox12/15 transgenic mice	Delayed atherosclerosis ↓ IL-17, CCL5, PGE2 ↑ PD1	[178]
	Alox12/15 deficient mice	Accelerated atherosclerosis ↑ IL-12p40, CCL5 ↓ LXA_4 production in macrophages	
Peritonitis	Alox12/15 deficient mice	↓ 14-HDHA	[179]
Arthritis	Alox12/15 deficient mice	↑ Inflammatory gene expression ↓ LXA_4 in inflamed synovia and macrophages	[180]
Collagen-induced arthritis		COX-2 product PGE_2 induces Alox12/15. PGE_2 stimulates resolution *via* LXA_4	[25]
Suture-induced chronic cornea injury	Alox12/15 deficient mice	↑ Inflammatory neovascularization	[181]
Peritonitis	Alox12/15 deficient mice	Resolution deficit caused by eosinophil depletion was rescued by eosinophil restoration or the administration of PD1. Eosinophils from Alox12/15 deficient mice could not rescue the resolution phenotype	[51]
Dermal fibrosis	Alox12/15 deficient mice	↑ TGF-β stimulated MAPK pathway LXA_4 counters TGF-β stimulated fibroblast activation	[182]
Endometriosis	Alox12/15 deficient mice	EPA administration decreased the number of lesions in controls but not in Alox12/15 deficient mice. Reduced levels of RvE3 after EPA administration in Alox12/15 deficient mice compared to control	[183]
Airway inflammation	Alox12/15 deficient mice	↓ TLR7-mediated resolution of airway inflammation	[184]
Peritonitis	Alox12/15 deficient mice	Low dose inhaled CO treatment reduces PMN infiltration in WT control, but failed to regulate PMN in Alox12/15 deficient mice	[185]

(B) 5-LOX deficient mice		
Cellular systems	**Actions/Phenotypes**	**References**
Respiratory Syncytial Virus (RSV)-induced bronchiolitis	↑ lung pathology Treatment of 5-LO(−/−) macrophages with LXA_4 and RvE1, but not LTB_4 or LTD_4, partially restored expression of alternatively activated Mϕ markers	[186]
Lyme arthritis (Borrelia burgdorferi infection)	earlier joint swelling and an inability to resolve arthritis ↓ Macrophage phagocytosis of *B. burgdorferi* and efferocytosis ↓ PMN uptake of opsonized spirochetes	[187]
Suture-induced cornea injury	↑ inflammatory neovascularization coincident with increased VEGF-A and FLT4 expression	[181]
Mycobacterium tuberculosis infection	↓ LXA_4 levels	[188]
Toxoplasma gondii infection	↓ LXA_4 levels	[189]

(B) 5-LOX deficient mice		
Cellular systems	**Actions/Phenotypes**	**References**
	↓ survival ↑ IL-12 and IFN-gamma	

Table 3

SPM receptors – Genetically modified mice

Receptor	LM Agonist	Genetic modification	Actions/phenotypes	References
ALX	LXA_4 RvD1	Transgenic mice	Accelerated resolution with LXA_4 and RvD1 in peritonitis	[56]
		Deficient mice	RvD1 action (e.g. PMN trafficking, miR and cytokine regulation) is reduced in peritonitis	[56]
		Deficient mice	RvD1 actions (reduction of PGE_2 and LTB_4) is abolished in peritonitis	[57]
		Deficient mice	Reduced protection of 15-epi-LXA_4 against intimal hyperplasia after carotid ligation	[190]
		Deficient mice	↑ disease severity (hypothermia and cardiac dysfunction) in sepsis ↓ monocyte recruitment	[191]
ChemR23	RvE1	Transgenic mice	Potentiated RvE1 actions in: ↓ PMN in peritonitis ↓ bone loss	[192]
		Transgenic mice	Heightened RvE1 response in: ↑ PMN phagocytosis of *P. gingivalis* ↓ PMN influx into the dorsal air pouch	[193]
BLT1	RvE1 (partial)	Deficient mice	RvE1 regulation of PMN infiltration is reduced	[194]

Table 4

SPM production in humans

SPM	Disease/tissues	Formation
Lipoxins & Aspirin-triggered lipoxins (ATL)	Asthma	Higher urinary ATL levels in aspirin-tolerant asthma than in aspirin-intolerant asthma [164, 195, 196] and regulate NK cell and innate lymphoid cell activation [165, 197]
	Alzheimer's disease (AD)	LXA_4 levels are reduced in AD brain and CSF [96]
	Colitis	Elevated mucosal LXA_4 promotes remission in Individuals with ulcerative colitis [171]
	Type 2 diabetes	Increased plasma ATL with intake of pioglitazone [198]
	Rheumatoid arthritis	LXA_4 in synovial fluid from rheumatoid arthritis patients [168]
	Localized aggressive periodontitis (LAP)	Less LXA_4 in LAP whole blood compared to healthy individuals [166]
	Peripheral artery disease	Plasma levels of ATL are lower in patients with symptomatic peripheral artery disease [199]
	Adipose tissues	LXA_4 identified in human adipocytes from obese patients [200]
	Milk	Lipoxins and resolvins at very high levels in the first month of lactation [132]
Resolvins	Synovial fluid	RvD5 present in synovial fluid from rheumatoid arthritis patients [168]
	Blood (healthy volunteers)	Plasma RvD1 and RvD2 identified with oral omega-3 supplementation [158]
	Adipose tissues	RvD1 and RvD2 identified in human adipocytes from obese patients [200]
	Human plasma and milk	RvE1 identified in human plasma [157] and milk [132]
	Multiple sclerosis	RvD1 was detected and upregulated in serum and cerebrospinal fluid in the highly active group [106]
	Human IgA nephropathy	RvE1 identified in patients supplemented with fish oil n-3 [201]
	Peripheral blood (plasma and serum), lymphoid organs	RvD1, RvD2 and RvD3, identified in amounts within their bioactive ranges [202]
Protectin	Asthma	PD1 in exhaled breath condensates in asthma exacerbation [169]; decreased PD1 in eosinophils from patients with severe asthma compared to healthy individuals [50]
	Embryonic stem cells	PD1 produced in embryonic stem cells [203]
	Multiple sclerosis	NPD1 was detected in serum and cerebrospinal fluid in the highly active group [106]
	Peripheral blood (plasma and serum), lymphoid organs	PD1 identified in amounts within their bioactive ranges. AT-PD1 is significantly increased with EFA and ASA intake [202]
Maresins	Synovial fluid	MaR1 identified in synovial fluid from arthritis patients [168]
	Peripheral blood (plasma and serum), lymphoid organs	MaR1 identified in amounts within their bioactive ranges [202]