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Review Series

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Resolvins in inflammation: emergence of the pro-resolving superfamily of mediators

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Countless times each day, the acute inflammatory response protects us from invading microbes, injuries, and insults from within, as in surgery-induced tissue injury. These challenges go unnoticed because they are self-limited and naturally resolve without progressing to chronic inflammation. Peripheral blood markers of inflammation are present in many common diseases, including inflammatory bowel disease, cardiovascular disease, neurodegenerative disease, and cancer. While acute inflammation is protective, excessive swarming of neutrophils amplifies collateral tissue damage and inflammation. Hence, understanding the mechanisms that control the resolution of acute inflammation provides insight into preventing and treating inflammatory diseases in multiple organs. This Review focuses on the resolution phase of inflammation with identification of specialized pro-resolving mediators (SPMs) that involve three separate biosynthetic and potent mediator families, which are defined using the first quantitative resolution indices to score this vital process. These are the resolvins, protectins, and maresins: bioactive metabolomes that each stimulate self-limited innate responses, enhance innate microbial killing and clearance, and are organ-protective. We briefly address biosynthesis of SPMs and their activation of endogenous resolution programs as terrain for new therapeutic approaches that are not, by definition, immunosuppressive, but rather new immunoresolvent therapies.

Protection versus uncontrolled inflammation: first responders and resolution

New evidence indicates that uncontrolled inflammation is a prominent component of many common diseases, including well-known inflammatory diseases such as arthritis and periodontal disease as well as inflammatory bowel disease, cardiovascular disease, the neurodegenerative diseases Alzheimer's and Parkinson's, asthma, cancer, metabolic syndromes (e.g., obesity), diabetes, and autoimmune diseases (<https://www.cdc.gov>). In each, peripheral blood markers of inflammation are present and elevated (1). Aging and proinflammatory nutrition (2, 3) also contribute to increases in inflammatory markers. Thus, the impact of uncontrolled inflammation on the United States alone is estimated in hundreds of millions of dollars for each disease, with substantial increases by 2030 — certainly, epidemic proportions.

The acute inflammatory response is protective. Among the first responders, neutrophils (polymorphonuclear leukocytes [PMNs]) leave postcapillary venules to phagocytize microbes and cellular debris (4). PMNs neutralize and clear invaders; however, when excess PMNs congregate or swarm in tissues

(5), they can inadvertently release their antimicrobial armamentarium via frustrated phagocytosis or cell death (4, 6), leading to tissue damage that amplifies inflammation and continues to chronicity. PMN-driven inflammation is a unifying mechanism for many diseases and reperfusion second-organ injury (4). Hence, it is critical to appreciate mechanisms and specialized mediators (7) involved in resolution and whether we can use these to control inflammation.

In health, acute inflammatory response(s) are self-limited, as in surgery-induced tissue injury, in that they resolve on their own and classically divide into initiation and resolution phases (4). To date, we view acute inflammation as a temporal crescendo to resolution and decrescendo of initiating chemical mediator gradients (7). In resolution (Figure 1), the host response is active (7) and not simply a passive dilution of proinflammatory mediators (8), enabling tissues to restore function (4). Lipoxins biosynthesized from arachidonic acid are potent, active stop signals for PMN infiltration (9, 10) and are produced during resolution of self-limited inflammatory responses (11, 12).

While current treatments for inflammation can be effective, many eventually become immunosuppressive opportunities for infection. Chemical mediators such as prostaglandins physiologically mediate the cardinal signs of inflammation (color, rubor, tumor, dolor) and are effectively controlled by traditional NSAIDs (13); however, NSAIDs are not without unwanted side effects. Given the significant public health impact of inflammation-associated diseases, it is paramount to seek new treatments and mechanisms controlling inflammation and collateral tissue damage from excessive PMN swarming (5). In

Conflict of interest: The authors are inventors on patent applications and awarded patents assigned to Brigham and Women's Hospital; some are licensed for clinical development (US patents 7,585,856; 6,670,396; 7,053,230; 7,709,669; 7,737,178; 8,349,896; 7,030,159; 7,741,368; 7,341,840; 7,803,557; 8,927,747; 9,611,238; 9,611,239; and 9,611,240 to CNS; and US patents 7,759,395; 7,872,152; 8,569,542; 8,933,270; 7,759,395; 7,872,152; 8,569,542; 8,273,792; 8,273,792; and 8,933,270 to CNS and BDL).

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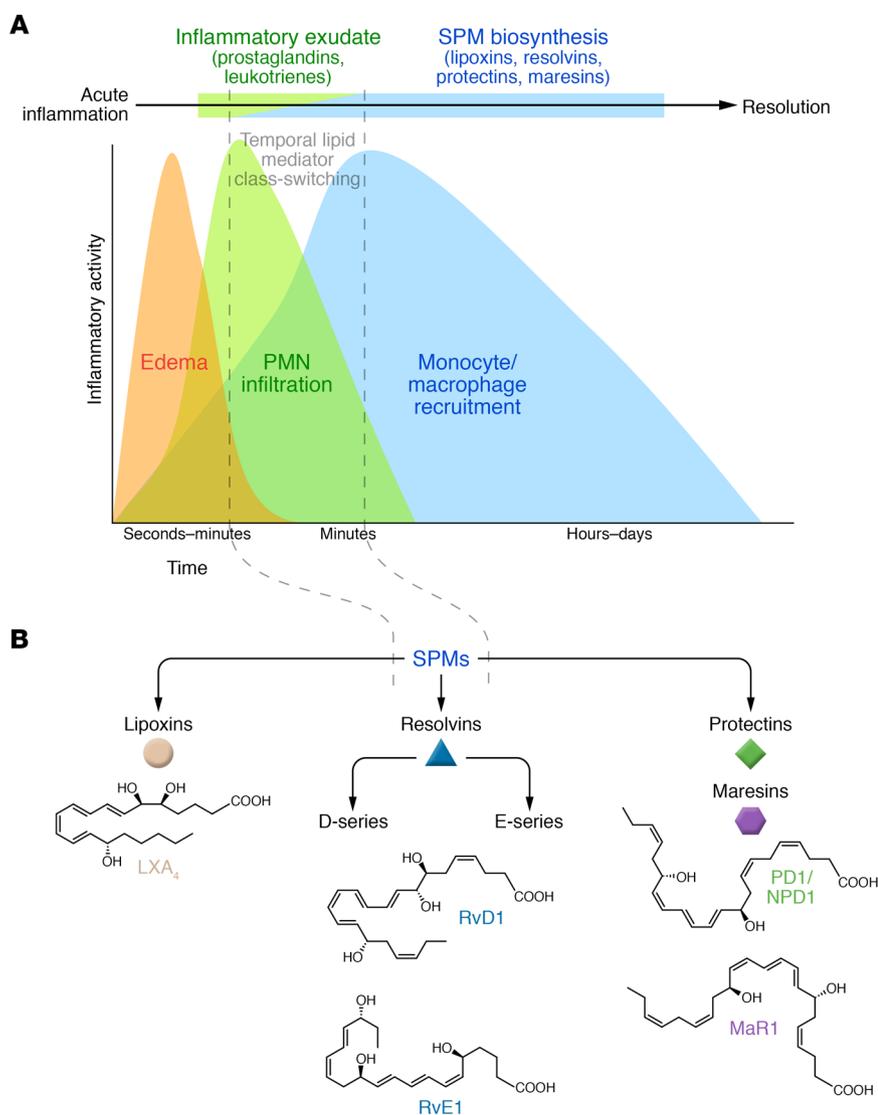


Figure 1. Acute inflammatory response and its ideal outcome: complete resolution. (A) Temporal lipid mediator class-switching initiates active resolution and SPM biosynthesis. Defined steps in the acute inflammation time course: edema, PMN infiltration, and then non-phlogistic monocyte-macrophage recruitment to inflammatory exudates. The reduction in PMN number coincides with the exudate appearance of SPMs and with the biosynthesis of lipoxins, resolvins (E- and D-series), protectins, and maresins in resolving exudates. **(B)** Each family of SPMs is structurally distinct and possesses potent pro-resolving actions.

this mini-series Review, we briefly address active endogenous resolution programs and novel resolution mediators as promising terrain for new therapeutic approaches (7) that would serve as immunoresolvents rather than immunosuppressants (14) — namely, pro-resolving agonists that stimulate resolution as pharmacologic agents (7, 15–18). We provide here a brief overview and update with key points from recent advances to complement other in-depth reviews (7, 15–17, 19, 20).

Specialized novel mediators in resolution

Chemical mediators govern cellular traffic, and those derived from essential polyunsaturated fatty acids (PUFAs) are most potent. Leukotriene B₄ (LTB₄) is a chemoattractant (21) and main mediator of PMN swarming (5). Using a systems approach, we

compared human pleural and PMN-rich exudates to time course studies from mouse air-pouch exudates and their resolution. We found a temporal lipid mediator class switch (11) where cyclooxygenase-derived prostaglandin E₂ (PGE₂) antecedes biosynthesis of lipoxins. Human PMNs exposed to PGE₂ or PGD₂ induced 15-lipoxygenase (15-LOX) switching phenotype from LTB₄ production to lipoxin production, which is a PMN stop signal that limits further recruitment (11). This PMN phenotype switch marks the resolution phase, because lipoxin A₄ (LXA₄) also stimulates macrophage efferocytosis (phagocytosis of apoptotic PMNs and debris) (6, 7, 18, 19). Using lipid mediator metabololipidomics, proteomics (liquid chromatography-tandem mass spectrometry [LC-MS/MS]), and cell trafficking in self-limited exudates, we identified three new families of mediators (9, 22–24), coined “resolvins” (short for resolution phase interaction products), “protectins,” and “maresins” (short for macrophage mediators in resolving inflammation) (25). Each is structurally distinct (Figure 2), biosynthesized from eicosapentaenoic acid (EPA), docosapentaenoic acid (n-3DPA), or docosahexaenoic acid (DHA) (7, 23, 26, 27). EPA-derived 18-HEPE and 15-HEPE are produced by hypoxic vascular endothelial cells and reduce PMN transendothelial migration, but are less potent than resolvin E1 (RvE1) or 15-epi-LXA₅ (9). Diapedesis or transendothelial migration is the committed step for PMN recruitment to inflamed sites (4). Both 18-HEPE and RvE1 are antiinflammatory, stopping PMN migration and stimulating resolution (9). Aspirin triggers their biosynthesis (Figure 2), and acetaminophen and indomethacin also permit 18-HEPE production, whereas selective cyclooxygenase-2 (COX-2) inhibitors block 18-HEPE production. These findings provided new mech-

anism(s) for aspirin’s well-appreciated benefits (19, 28). It was deemed critical to establish defining criteria for pro-resolving actions to qualify and validate these new molecules to direct elucidation of biosynthesis and structure (Table 1).

In addition to biosynthesis of lipoxins and their aspirin-triggered 15-epimeric forms (reviewed in ref. 19), newer n-3 PUFA-derived bioactive metabolomes for resolvins, protectins, and maresins (7) are depicted in Figure 2. Because each family member possesses potent pro-resolving and antiinflammatory actions (recently reviewed in refs. 7, 29) with special functions in the resolution phase (Table 1), this superfamily is coined “specialized pro-resolving mediators” (SPMs). Each carries defining biological functions with cell type- and organ-specific properties, reflecting stereospecific activation of cellular receptors (30). The

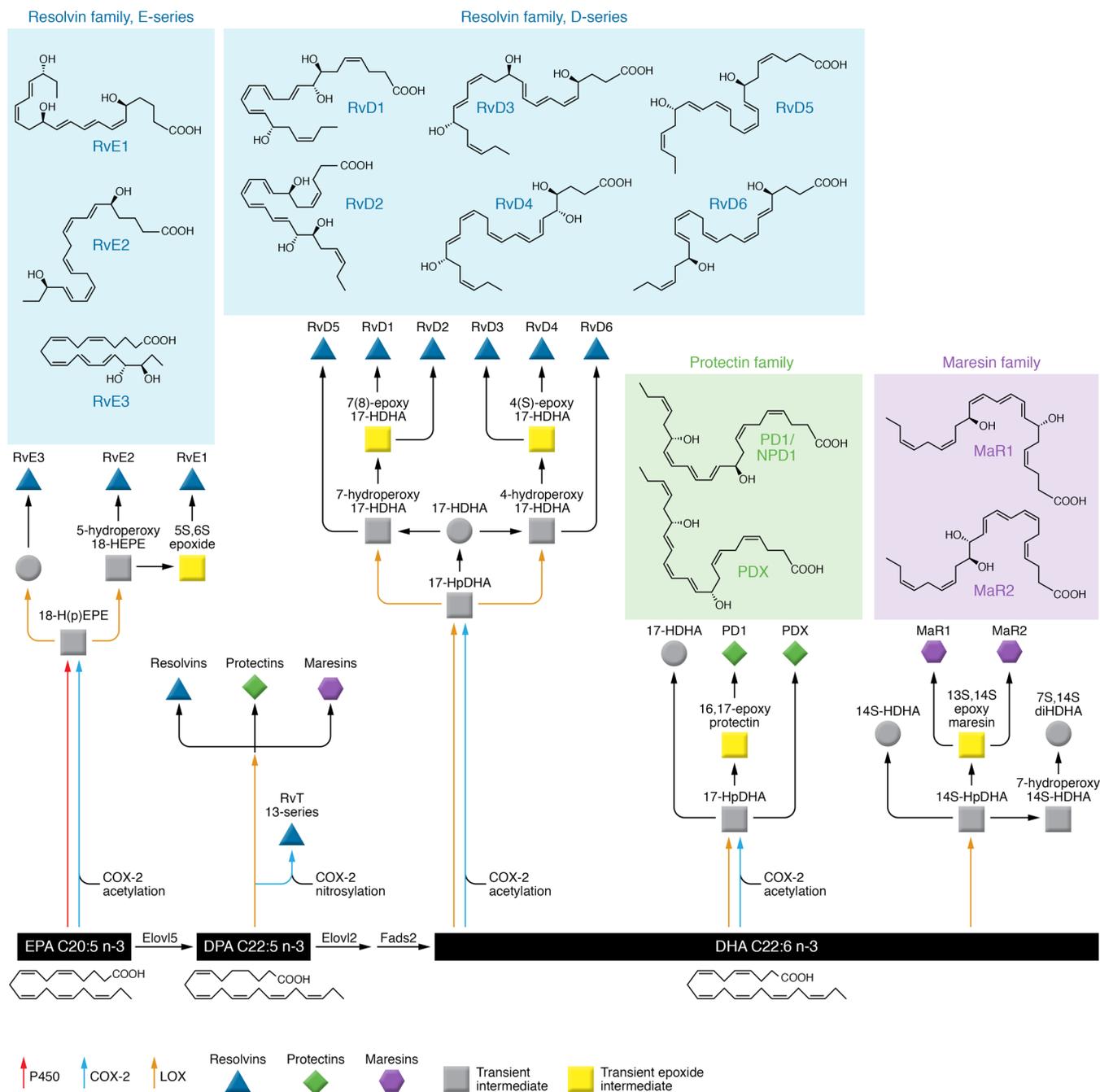


Figure 2. SPM network biosynthetic metabolomes. Network illustration of the enzymes, intermediates, and precursors of the SPM superfamily’s biosynthesis from omega-3 PUFA. Deficiencies in the fatty acid desaturase (Fads) gene cluster reduce SPM production (194). Stereochemistry of each major SPM is established; for detailed mechanisms in biosynthesis and complete SPM nomenclature of each endogenous molecule, see refs. 36, 39, 41–43, and 58 and those within.

main biosynthesis routes were each confirmed via trapping of intermediates and label-tracking of precursors and intermediates. In addition to lipoxygenase-initiated pathways that produce mediators with alcohols, e.g., PD1/NPD1 or D-series resolvins (RvDs) in predominantly 17S configuration, aspirin acetylation of COX-2 produces intermediates in the R configuration at the 17-carbon position, giving 17R epimers or 17R-PD1 and RvDs, coined as aspirin-triggered protectin and resolvin mediators (23, 31). SPM R-epimers are longer-acting. Statins also lead to COX-2 S-nitrosylation that,

like aspirin, changes the enzyme’s catalysis to produce predominantly R-epimer-containing intermediates, exemplified by novel 13-series resolvins (RvTs) from vascular n-3DPA (26). The complete stereochemistry and biosynthesis of each SPM are established (32–43), as are epoxy-intermediates of maresins and protectins (36).

Resolvins are produced from DHA, n-3DPA, and EPA (Figure 2), marine oils that enter humans via nutrition or supplementation (3). The term “resolvin” refers to the unique structures, temporal code in biosynthesis during resolution, and potent pico-nanogram

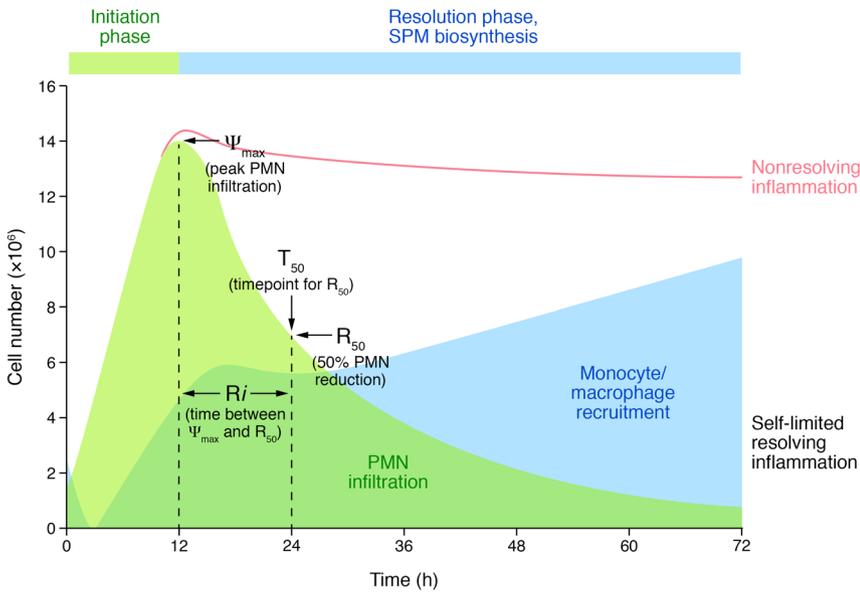


Figure 3. Quantitative definition of exudate resolution and non-resolving inflammation. Hypothetical example of contained self-limited resolving inflammation versus non-resolving inflammation (red line) to illustrate the quantitative indices and components: ψ_{max} for peak PMN infiltration, 50% of peak PMN (R_{50}), time point of R_{50} (T_{50}), and resolution interval (R_i) to quantify PMN influx and removal as well as non-phlogistic recruitment of monocytes-macrophages in exudates, which is required for repair and renewed function. See text and refs. 22 and 85 for original results and definitions.

ability to counterregulate proinflammatories and actively promote resolution via monocyte/macrophage uptake of debris, apoptotic PMNs, and killing/clearing microbes (23, 37, 38). RvEs from EPA (18-HEPE, RvE1, RvE2, and RvE3) have four main bioactive mediators, biosynthesized as either 18R or 18S epimers (38) with activity in pico-nanogram ranges that is not shared by their precursor EPA. RvE1 downregulates leukocyte adhesive molecules (i.e., CD11/CD18) and ADP-dependent platelet activation (44, 45). RvE1 promotes PMN apoptosis to accelerate resolution (46). Human PMN RvE2 biosynthesis is enhanced in hypoxia (47), 18-HEPE is cardioprotective (48), and RvE3 stops PMNs (49). RvE1 reduces dendritic cells' IL-12 production (32) and, in skin, attenuates contact hypersensitivity (50). RvE1 and RvE2 biosynthesis involves 5-LOX, pro-

ducing an 18-hydroxy-5(6)-epoxide via LTA_4 hydrolase that is converted to RvE1, and 5-LOX converts 18-HEPE to RvE2; RvE1 and RvE2 each potentially stimulate IL-10 and phagocytosis (38, 51).

RvD1-RvD6 are biosynthesized in exudates and by human PMNs and macrophages (23, 52) via two separate allylic epoxide-containing intermediates (Figure 2). RvD1 and RvD2 are biosynthesized from a 17-hydroperoxy product of 15-LOX with substrate DHA. This intermediate is converted to either 7(8)-epoxytetraene-intermediate or RvD5 via 5-LOX (35). RvD2 also carries potent organ-protective actions and enhances bacterial killing/clearance (53). RvD1 protects from PMN-mediated reperfusion organ injury (54). In exudates, RvD1 and RvD2 appear in the onset of resolution followed by RvD3 and RvD4 from a 4(5)epoxide-intermediate (14, 55, 56). Each stereochemistry is confirmed (14, 39, 55-57).

Protectin biosynthesis and maresin biosynthesis (Figure 2) each proceed via epoxide intermediates critical to attain the stereochemistry of their potent mediators (58). Protectin D1 (PD1) is enzymatically produced by human leukocytes from 16(17)epoxide-intermediate (34). In addition to PMNs, macrophages (34, 52) and eosinophils (59, 60) produce PD1, and its production is reduced in patients with severe asthma (61, 62). The double lipoxygenase product 10,17-diHDHA is obtained by two sequential steps with reduction of hydroperoxide-intermediate(s) giving 10S,17S-diHETE (34) coined PDX, an isomer of PD1, which has several actions (63-66) but whose receptor remains unknown. PD1 when produced in neural systems is termed neuroprotectin D1 (NPD1/PD1) and demonstrates potent protective actions in retina, brain, and pain (67, 68).

Maresin biosynthesis is initiated at carbon-14 via human 12-LOX (25, 69), producing a 13(14)epoxide-intermediate (eMaR) that stimulates M1 conversion to M2 macrophages and blocks LTA_4 hydrolase (70). The stereochemistry of the products maresin 1 (MaR1) and MaR2 is established, with actions in pain and tissue regeneration (33, 70).

Substrate flow. Resolving secretory phospholipases, sPLA2-IIID and sPLA2-III, release DHA and n-3DPA from phospholipids with selectivity for SPM production (71). Microparticles are also a source of SPM precursors, e.g., 17-HDHA released via sPLA2 (52, 72). These substrates are taken up via nutrition and esterified into phospholipids. The ratio of n-3 to n-6 is currently used to mark human levels of omega-3 fatty acids obtained from algae and marine organisms as potential membrane sources of SPMs (3, 73, 74). Omega-3 fatty acids were thought to block coagulation; however, doses up to 10 g/d EPA and DHA or consumption of 1.5 g/d for 52 weeks by cancer or ICU patients were found to be safe and without adverse bleeding (75). During resolution of inflammation, non-esterified substrates also flow into exudates via edema carried by proteins (54), which appears to be the major substrate form supplied to the brain (76).

Table 1. Pro-resolving mediators: defining physiologic actions in the signs of resolution

Temporal stereospecific biosynthesis via leukocyte exudate traffic
Cessation of PMN infiltration; stop signals to limit further PMN recruitment and PMN-mediated tissue damage
Enhancement of macrophage phagocytosis of apoptotic PMNs and cellular debris and augmentation of bacteria killing by phagocytes
Actions at both transcriptional and translational level, microRNA
Actions via specific receptors in the pico-nanomolar range in a stereoselective fashion
Shortening of time to resolution (resolution interval R_i) by activation of endogenous resolution programs
Resolution and reduction of pain

While appreciated as an intermediate in n-3 PUFA biosynthesis in humans, n-3DPA conversion to DHA appears to be greater in women than men supplemented with α -linolenic acid (77). n-3DPA is also a precursor to SPMs, carrying 22 carbons with 5 double bonds (denoted C22:5; Figure 2) as opposed to 6 in DHA (C22:6) (27). These n-3 immunoresolvents are biosynthesized (Figure 2) in three families: resolvin_{n-3DPA}, protectin_{n-3DPA}, and maresin_{n-3DPA}, each demonstrating potent pro-resolving actions (27) in human subjects (78). Rapid advances in the organic synthesis of SPMs from n-3DPA and their matching to endogenous mediators (36, 79) facilitated demonstration of potent protection by protectin D1_{n-3DPA} and resolvin D5_{n-3DPA} in colitis (80). Human and mouse tissues treated with the statin atorvastatin convert n-3DPA to RvTs (26). RvTs are organ-protective, enhance phagocytosis and bacterial killing, and regulate inflammasome components. This mechanism involves COX-2 S-nitrosylation and transcellular RvT biosynthesis via PMN-endothelial cell interactions that accelerate resolution; RvTs are produced in healthy subjects (26). RvTs activate protective host responses to resolve infection-initiated inflammation (26) and, like resolvins and protectins (58, 81), uncover a potential approach to develop host-directed therapies (82).

In addition to transcellular mechanisms, SPM biosynthesis proceeds via HDL interactions with macrophages (83), producing LXB₄ and RvE2 from healthy subjects. Macrophages also produce SPMs when interacting with apoptotic PMNs (52) and pro-resolving microparticles (72).

Resolution indices: quantitative definitions for physiology and pharmacology

Once it was established that lipoxins, aspirin-triggered lipoxins, and their synthetic analogs are antiinflammatory (7, 81), a quantitative definition of resolution was needed to account for cellular and molecular mechanisms of novel pro-resolving mediators, because resolution was described only by histology (4, 84). This was critical because in self-limited inflammation, the ideal outcome is resolution, a highly coordinated and active process controlled by pro-resolving mediators (84). In addition to pinpointing SPM biosynthesis and actions (Figure 3), resolution indices can also dissect the impact of drugs and infection. Charles Serhan's laboratory introduced quantitative resolution indices focusing on exudate PMNs and macrophages. Quantitation of PMN infiltration, subsequent clearance by apoptosis and efferocytosis, and non-phlogistic monocyte/macrophage recruitment, including their magnitude, duration, and loss from exudates (22, 85), gave birth to the resolution interval (R_i , time interval from maximum PMN influx point Ψ_{\max} to 50% reduction R_{50} , i.e., $T_{50} - T_{\max}$; Figure 3). Resolution indices defined inflammatory catabasis using temporal lipidomics, proteomics, and flow cytometry to establish relationships between eicosanoids, SPMs, and chemokines/cytokines, as well as potential resolver or protein resolution activators (22, 37, 85). Among the identified resolver proteins are annexin A1 and annexin I-derived peptides that stimulate resolution (17).

SPMs shorten R_i both by lowering the amplitude of PMN influx (Ψ_{\max}) and by stimulating clearance by efferocytosis and phagocytosis, microbe killing, and containment (14, 37, 86). These indices permitted assignment of roles of additional resolution agonists such as erythropoietin (87), plasmin (88), carbon

monoxide (89), cyclin-dependent kinase inhibitors (90), annexin peptides (91), and others (17). Since these indices were unavailable at the time of development, some widely used drugs are now recognized as "resolution toxic," i.e., disrupting active resolution programs (20) including NSAIDs and COX-2 inhibitors. These antiinflammatories lower PMN amplitude (Ψ_{\max}) but lengthen resolution interval (R_i) by impairing efferocytosis and/or uncoupling PGE₂- and PGD₂-dependent lipoxygenase expression (11, 92, 93). Lipoxygenase inhibitors also increase R_i by decreasing SPMs (85), and lidocaine increases R_i by blocking efferocytosis (94). In contrast, some widely used drugs stimulate resolution and shorten R_i . Distinct from NSAIDs, aspirin decreases R_i by acetylating COX-2, contributing to production of the R-epimer lipoxins, resolvins, and protectins (7, 31). Other common resolution-promoting drugs include statins, which increase epimeric SPMs (26), and glucocorticoids, which increase annexin A1 (95) and apoptosis as well as efferocytosis (20) yet can turn immunosuppressive. Hence, resolution indices defined the resolution agonist (Figure 3) properties of resolvins and other SPMs (Figure 2), which are critical for developing new therapeutics that are resolution-friendly. Antiinflammatories clearly have a different mechanism of action than immunoresolvents (Table 1).

SPMs promote resolution in sterile versus infectious inflammation

Specific SPMs are temporally and differentially regulated during infections and sterile tissue responses to injury. With bacterial infection, SPMs display anti-phlogistic properties and enhance pathogen containment. In contrast to immunosuppression, SPM augmentation of host defense lowers antibiotic requirements for bacterial clearance. Interestingly, RvD1 and RvD5 reduce bacterial titers in blood and exudates, in part by increasing neutrophil and macrophage phagocytosis of bacteria and mediating counterregulation of proinflammatory genes, including those encoding NF- κ B and TNF- α (37). Both RvD1 and ciprofloxacin accelerate resolution of *E. coli* infection, shortening R_i ; moreover, RvD1's host-directed actions enhance ciprofloxacin's therapeutic effects (37, 96). RvD2 is another potent immunoresolvent that is biosynthesized during active tissue resolution programs (53). In both *E. coli* and *Staphylococcus aureus* infections, RvD2 limits neutrophil infiltration and enhances phagocyte clearance of bacteria (97). In addition to regulating neutrophil responses to infection, RvD2 mediates protection from neutrophil-initiated second-organ injury. After sterile injury from ischemia/reperfusion, RvD2 gives marked organ protection with decreased neutrophil infiltration to lungs. In this model, RvD2 administration increases tissue levels of other SPMs in a receptor-mediated manner to propel a positive-feedback loop for resolution (97).

In addition to leukocyte-mediated injury "from within," sterile direct tissue injury by extrinsic means evokes a resolution response in health. In mouse lung injury from gastric acid aspiration, SPM production is temporally regulated with early MaR1 and later RvD1 and RvD3 (98–100). Intravenous administration of MaR1, RvD1, or RvD3 after intrabronchial acid dampens the maximal extent of acute lung inflammation and promotes a more rapid return to homeostasis. RvD1 also protects tissue after hyperoxic lung injury, decreasing oxidative stress and NF- κ B. SPMs, includ-

ing RvD1 and MaR1, can also shorten R_i for lung injury by increasing macrophage heme oxygenase-1 (89, 101). In these models, SPMs mediate protection via several cellular and organ-level mechanisms, including decreasing neutrophil trafficking and activation, increasing macrophage phagocytosis and efferocytosis, accelerating restitution of epithelial barrier integrity, and enhancing edema clearance (102).

SPMs in transitions between innate and adaptive immunity

Beyond innate phagocyte responses to resolve acute inflammation, SPMs appear to play critical roles in regulating adaptive immunity. While homeostatic adaptive immune responses are targeted, pathologic adaptive inflammation can become overly exuberant or chronic and nonresolving. SPMs selectively regulate cytokines via SPM receptors expressed on innate lymphoid, NK, T, and B cells. In type 2 innate lymphoid cells, SPMs decrease proinflammatory type 2 cytokine production but increase amphiregulin expression for mucosal protection (103, 104). Cytotoxic properties of NK cells can promote granulocyte apoptosis for their clearance, a resolution mechanism augmented by SPMs (103). RvD1 and RvD2 control CD4⁺ T cell differentiation into Th1 and Th17 effectors with decreased production of the lineage-specific cytokines IFN- γ (Th1) and IL-17 (Th17) and their transcription factors T-bet and RORc (105). SPMs also decrease production of IL-2, IFN- γ , and TNF- α by CD8⁺ T cells.

To regulate adaptive responses, SPMs such as MaR1 promote de novo generation of FoxP3-expressing regulatory T cells from naive CD4⁺ T cells as well as TGF- β and amphiregulin expression (104). SPMs have an adjuvant effect on B cells, enhancing humoral immunity. SPMs increase IgM and IgG production from activated human B cells with differentiation toward a CD27⁺CD38⁺ antibody-secreting cell phenotype (106). Also, SPMs target B cell epsilon germline transcript to selectively inhibit IgE without decreasing IgM and IgG or IgA production (107).

SPM receptors and intracellular signaling

To mediate cell type-specific actions, SPMs principally serve as ligands for select surface receptors. To date, four human SPM receptors are identified: ALX/FPR2, ERV1, DRV1, and DRV2. While named for the ligand used for identification (LXA₄, RvE1, RvD1, and RvD2, respectively), each receptor is capable of interacting with additional SPMs (30). RvD1, for example, interacts with ALX/FPR2 and DRV1 in a context-specific manner. In response to an inflammatory stimulus, neutrophils rapidly mobilize ALX/FPR2, but not DRV1, from secretory granules to cell membranes, so RvD1 interacts with DRV1 for homeostatic functions and with ALX/FPR2 for antineutrophil actions in resolving inflammation (108, 109). Notably, in some instances, SPMs display receptor-level antagonism at pro-phlogistic receptors. This antagonism is exemplified by inhibition of interactions of LTB₄ with its receptor BLT1 by RvE1 and MaR1 (110, 111).

ALX/FPR2 receptors are broadly expressed and engaged by SPMs and peptides at distinct domains to influence intracellular signaling and cell functional responses. Interestingly, the acute-phase protein serum amyloid A (SAA) can engage ALX/FPR2 receptors (112). When the counter-ligand is present in excess,

SAA and the SPM ligands allosterically inhibit each other to bias ALX/FPR2 signaling to promote either inflammation (SAA) or resolution (SPM) (113), suggesting a pivotal role for these receptors in the temporal course of an inflammatory response. ALX/FPR2 receptors can dimerize to alter ligand-dependent intracellular signaling (114). SAA interactions with ALX/FPR2 decrease formation of homodimers. In contrast, SPM engagement increases both ALX/FPR2 homodimerization and heterodimerization with FPR1 receptor. ALX/FPR2-FPR1 heterodimers have distinct downstream signaling events, with phosphorylation of the JNK/caspase-3 pathway and proapoptotic signaling pathways.

LXA₄ can also serve as an endogenous allosteric regulator of the endocannabinoid receptor CB1 (115). ERV1 receptors are also able to interact with both peptide and lipid ligands, chemerin and RvE1, respectively (32). As with ALX/FPR2, peptide and SPM signaling events by this receptor have distinct patterns of activation for intracellular pathways, including ERK and NF- κ B phosphorylation (46). SPM interactions with ALX/FPR2 and ERV1 decrease NF- κ B activity and cytokine production (46, 116). Translocation of NF- κ B to the nucleus and its activity are also regulated by SPM signaling at DRV1 and DRV2 (97, 100, 117). In another feed-forward mechanism for resolution, SPM receptor signaling by one mediator can promote expression of additional SPMs for other SPM receptors, exemplified by RvE1-ERV1 signaling promoting increased biosynthesis of LXA₄ for ALX/FPR2-mediated resolution of allergic lung inflammation (118), and RvD2-DRV2 induction of RvD5 and PD1 for resolution of ischemia/reperfusion injury (37).

SPM receptor activation of intracellular signaling is cell type- and organ-specific; however, a few common themes emerge from existing results. Distinct ligand binding can influence receptor dimerization with alternate patterns of intracellular signal coupling to evoke specific phosphorylation cascades (114), polyisoprenyl phosphate remodeling (119), and microRNA expression patterns that together dictate cellular functional responses. Also, resolvin receptor activation signals specific microRNAs that carry sustained tissue responses (120–122).

Neural systems and arthritic pain

Human brain tissues produce RvD1, PD1, and MaR1 (123, 124). LXA₄, MaR1, RvD1, NPD1, and PDX show neuroprotective activities. MaR1 and RvD1 downregulate β -amyloid-initiated inflammation with human microglia, suggesting a role for SPMs in neural tissues (123). MaR1 stimulates phagocytosis of the amyloid peptide A β ₄₂ (123), as does RvD1 (125) with lower SPM levels in Alzheimer's disease (126). MaR1 is neuroprotective in murine spinal cord injury, enabling functional recovery (127). DHA and NPD1 are neuroprotective in the retina (128), CNS, and brain (68), and PD1/NPD1 and resolvins may protect in early-stage Alzheimer's as well as in ischemic stroke (124, 129). Microglial cell production of proinflammatory cytokines is selectively reduced by SPMs (23, 24), with increased production of antiinflammatory IL-10 (130). In stress models, RvD1 and RvD2 prevent depression-like behaviors, and nanogram doses give sustained antidepressant effects (131, 132). Since it was first demonstrated that RvE1 and RvD1 are potent in resolving inflammatory and postoperative pain (133, 134) and that their receptors can regulate transient receptor potential (TRP) ion channels and spinal cord synaptic transmission, addi-

tional resolvins (RvD2), protectins, and MaR1 (Figure 2) were shown to display potent ability to reduce inflammatory pain without altering motor functions or baseline pain (33, 135). RvE1 selectively blocks TRPV1 ($IC_{50} = 1$ nM), RvD1 acts via TRPA1 ($IC_{50} = 9$ nM), and RvD2 acts via TRPV1 ($IC_{50} = 0.1$ nM) and TRPA1 ($IC_{50} = 2$ nM) (136). RvE1 inhibits substance P actions on peripheral nociceptive neurons (137). AT-RvD1 also mitigates motor and cognitive deficits in diffuse brain injury, and RvE1 increases posttraumatic sleep (138).

AT-RvD1 reduces osteoarthritic pain (139), as does precursor 17-HDHA (140), prompting validation of their receptors (ALX/FPR2 and ERV/CMKLR1) in rat models of osteoarthritis pain (141). Plasma RvD2 levels correlate with reduction in astrogliosis in spinal cord (141). Fish consumption by humans, which increases plasma SPMs and precursors, reduces rheumatoid arthritis (RA) disease activity (142), and omega-3 fatty acid supplementation increases 18-HEPE and 17-HDHA, as well as RvEs, PD1, PDX, MaR1, and RvDs in plasma and synovial fluid (143). In synovial fluids, RvE2 increases are associated with reduced pain in arthritic patients (143). RvD1 and RvD3 are present in human arthritic synovial fluids (144, 145) and are protective in mouse arthritis, suggesting that increasing local joint SPMs may reduce RA pain. In human osteoarthritis pain, circulating 17-HDHA is associated with lower pain scores; however, circulating resolvins were below limits of detection (146). Vagal stimulation reduces arthritic joint inflammation in humans (147), and vagotomy in mice reduces pro-resolving mediators (i.e., SPMs, lipoxins, and netrin-1, an axonal guidance protein) that stimulate human monocytes to produce resolvins and lipoxins. The vagus nerve controls inflammation amplitude (147) by regulating SPMs and resolution (148). Acetylcholine from the vagus nerve induces 15-LOX-1 in type 3 innate lymphoid cells to produce protectins (i.e., PCTR1) that reduce infections (149). PCTRs and other new SPM sulfido-conjugates in tissue regeneration and their relation to leukotrienes were recently reviewed (15). Hence, plasticity of neural networks and their innate immune system interactions are regulated by specific SPMs.

Fish to human resolvins, protectin, and maresin production

SPMs can be produced in many human target organs (7). Availability of SPM synthetic standards, deuterium-labeled SPMs, and targeted LC-MS/MS (150) now permits identification of resolvins, protectins, and maresins in human tissues. In addition to substrates, trout brain (151) and salmon tissues contain resolvins (152), indicating that SPMs are conserved structures in evolution. In humans, SPMs are identified in several types of human specimens and biomatrices. PD1 is in exhaled breath condensates (61), RvE1 is in plasma (32), and RvD1 and RvD2 are in serum (153, 154). Lymph nodes, spleen, and serum possess most species of SPMs (150). Human spleen has RvD5, PD1, and MaR1, as well as RvE1, RvE2, RvE3, and LXA₄; human axillary lymph nodes carry RvD1, RvD5, RvD6, RvE3, and lipoxins (150).

Mounting evidence indicates that SPM production is altered and often diminished in affected tissues and in circulation across a spectrum of chronic inflammatory diseases. In this context, in human synovial fluid from RA patients, RvD1, 17-epi-RvD1, RvD2, RvD3, RvE1, RvE2, RvE3, PD1, MaR1, 17-HDHA, and 18-HEPE are

present (143-145), and RvD3 is reduced in serum from RA patients (144). RvD1 is sharply reduced in vulnerable regions of human atherosclerotic plaques (155), and, in omental adipose tissue from obese patients, RvDs, RvEs, PD1, MaR1, and lipoxins are reduced relative to LTB₄ and prostaglandins (101). In brain and cerebrospinal fluid from Alzheimer's disease patients, RvD1 and LXA₄ are decreased (123, 126). Specific SPMs are present in human urine, namely RvD1, 17-epi-RvD1, and RvE2, which are decreased in smokers (156).

Recently, RvDs, PD1, and lipoxins were identified in human emotional tears with sex-specific levels that are reduced in females (40). RvDs are present in human skin blisters and increased in females (157). Healthy subjects' recovery phase from strenuous exercise is characterized by increases in serum RvD1, RvE1, LXA₄, and LXB₄, which are blocked when subjects are pretreated with ibuprofen (93). In patients with chronic daily headaches, dietary omega-3 intervention increases plasma resolvins, 17-HDHA, and 18-HEPE with concomitant reduction in headache pain (158). In sepsis, plasma RvE1, RvD5, and 17-epi-PD1 increase in nonsurvivors relative to survivors and are potential biomarkers for critical illness (159). At birth, SPMs are present in human umbilical cord blood (RvE1, RvE2, RvE3, RvD1, 17-epi-RvD1, RvD2, 17-HDHA, and 18-HEPE) (160, 161), and placenta carries RvD1, 17-epi-RvD1, RvD2, PD1, 17-HDHA, and 18-HEPE (162). Prenatal n-3 supplementation increases 18-HEPE and 17-HDHA concentrations in human maternal and cord blood (160, 163), as well as in placenta (163), possibly supporting early immune functions (164). Along these lines, human breast milk contains bioactive SPM clusters consisting of RvD1, RvD2, RvD3, 17-epi-RvD3, RvD4, PD1, MaR1, RvE1, RvE2, RvE3, LXA₄, LXB₄, 17-HDHA, and 18-HEPE (165, 166), is a potential source of maternal-infant omega-3 and SPM transfer, and links to beneficial maternal n-3 supplementation during pregnancy with decreased incidence in children of asthma and respiratory infections (167), food allergy, and eczema (164).

Hence, specific SPMs and SPM clusters are present at biologically active amounts in human inflammatory exudates, physiologic tissues, and fluids as demonstrated by targeted LC-MS/MS-based approaches. In human peripheral blood, several laboratories collectively identified plasma SPMs (38, 168), as well as a plasma SPM cluster consisting of RvE1, RvE2, RvD1, 17-epi-RvD1, RvD2, RvD5, RvD6, PD1, 17-HDHA, and 18-HEPE (150, 153), and a serum cluster of RvD1, 17-epi-RvD1, RvD2, RvD3, PD1, MaR1, RvE1, and RvE2. SPM concentrations attained in human peripheral blood target PMNs and monocytes (at the single-cell level determined by CyTOF mass cytometry) to increase phagocytosis and killing of *E. coli* (116). PUFAs are associated with reduced incidence of fatal coronary heart disease (169, 170), and it has recently been established that omega-3 supplementation at doses up to 10 g/d (EPA and DHA) does not increase risk of bleeding or affect other coagulation parameters (75).

In human saliva, the leukotriene/RvD1 ratio predicts vascular disease (171), and saliva SPMs in aggressive periodontal disease may be useful for monitoring disease status (172). Randomized trials showed that alcohol consumption increases specific plasma SPMs: 18-HEPE, RvD1, and 17R-RvD1 (173). In obese women, 1.8 g daily EPA and DHA supplementation increased resolvins in plasma (174) and in lungs during acute respiratory distress syndrome (175). Thus, it appears that in certain organs, dietary n-3

Table 2. SPM immunoresolvents in disease

SPM	Disease model	Reference
RvE1	Periodontal disease, dysbiosis	195
	Lung injury	46
RvE1	Colitis	196
	Acid-induced lung injury	102
RvD5, PD1	<i>E. coli</i> infection	37
RvD2	Cecal ligation and puncture sepsis	53, 117
RvD2	Burn wound sepsis	197
RvD3	Aging mice, peritonitis	86
RvD4	Skin inflammation, peritonitis, organ protection	56, 57
RvD1, RvD3	Arthritis	144, 145
RvE1, RvD1, and RvD2	Cancer	189, 190, 198, 199
RvE1	Obesity	193
Lipoxins and resolvins	Neuroinflammation	120
	Postoperative cognitive decline	185
	Atherosclerosis	200
	Asthma	118

increases tissue SPMs, and that not all SPMs (Figure 2) are produced in each organ, save resolving exudates. Also, some human tissues and fluids, e.g., breast milk, placenta, lymph nodes, lung, and tears, may constitutively biosynthesize SPMs, while others, such as blood (116) and spleen (176), produce SPMs upon cell activation. Now that these procedures are available, additional human studies are needed to investigate the role of organ-specific SPM production and actions in human tissues.

Novel therapeutics: SPM inactivation and metabolically stable mimetics

While some resolvins and other SPMs reach circulation (150, 159), most are metabolically inactivated at local sites of inflammation (168). For example, RvE1 is converted via an eicosanoid oxidoreductase (EOR, specifically prostaglandin dehydrogenase) (177) to inactive 18-oxo-RvE1. Stable analogs of RvE1 that prevent dehydrogenation at carbon-18 are longer-acting, demonstrating potent mimetic actions of RvE1 in pain and inflammation (134, 168). RvD1 is also subject to dehydrogenation via EOR at carbon-17 alcohol to inactive 17-oxo-RvD1 (35). Stable RvD1 analogs that prevent rapid dehydrogenation at carbon-17 are potent mimetics (54). RvD4, RvD5, and MaR1 are also subject to local metabolism to oxo-products (37, 56, 111). Nanomedicines were designed that deliver SPMs and their analogs (72) and with unidirectional sustained delivery (178). A benzo-RvD1 analog was designed to retain RvD1's pro-resolving actions, requiring fewer steps in organic synthesis by eliminating the tetraene conjugation, which is less potent

(179). An RvE1 analog was successful in human clinical trial for dry eye inflammation (180, 181), and another pro-resolving stable SPM analog is currently in trial for periodontal inflammation (182). Several of these molecules are in clinical development programs. Given the number of SPMs and their potencies in multiple organs, investigation of mimetics and/or metabolically stable analogs of SPMs (Figure 2) could reveal their potential in promoting resolution of pathologic inflammation, addressing resolution defects that are present in many human diseases.

Therapeutic opportunities for SPM mechanisms

SPMs have proven potent pro-resolving actions in a range of disease models (Table 2); given their potency, many drug development opportunities are possible. Human PMN swarming activates a temporal biosynthetic code that produces stop signals, e.g., LXA₄ and resolvins, at critical PMN densities (183). Temporal biosynthesis with lipid mediator class switching is documented in human blisters (157) and with specific drugs (184) (e.g., dexmedetomidine) that can prevent cognitive decline by activating SPMs (185). In randomized trials, immunonutrition (dietary interventions that modulate the immune system) increases RvE1 in patients undergoing hepatobiliary surgery, giving lower rates of infection complications and severity (186). Treating coronary artery disease patients with Lovaza resurrects SPM production (187). Enhancing SPMs via substrate supplementation may also improve outcomes in military personnel and in traumatic brain injury (188). Building on the ability of SPMs to clear debris, resolving cancer inflammation with RvE1, RvD1, or RvD2 reduces chemotherapy-initiated tumor debris and lowers dose requirements for cancer drugs (189) by stimulating resolution macrophages (190). Western diet triggers inflammasome-mediated trained immunity with heightened inflammation (191). RvT and lipoxin reduce inflammasome activation (26, 192), suggesting that SPMs can help control obesity (193) and other diseases in which inflammation is excessive (Table 2). The recent identification of a third phase of acute inflammation that arcs into adaptive immunity (16) supplies new targets and opportunities. In addition to innate immunity, RvD1, RvD2, and RvE1 target T and B lymphocytes (105, 107), widening the scope and potential for SPM-based therapeutics and resolution physiology/pharmacology.

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