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Specialized Pro-Resolving Mediator Network: An Update on Production and Actions*

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Abstract

Today, persistent and uncontrolled inflammation is appreciated to play a pivotal role in many diseases, such as cardiovascular disease, neurodegenerative diseases, metabolic syndrome, and many other diseases of public health concern (e.g. COVID-19 and periodontal disease). The ideal response to initial challenge in humans is a self-limited inflammatory response leading to complete resolution. The resolution phase is now widely recognized as a biosynthetically active process, governed by a superfamily of endogenous chemical mediators that stimulate resolution of inflammatory responses, namely specialized proresolving mediators (SPMs). Because resolution is the natural ideal response, the SPMs have gained attention. SPMs are mediators that include omege-6 arachidonic acid-derived lipoxins, omega-3 EPA and DHA derived resolvins, protectins and maresins, cysteinyl-SPMs, as well as n-3 DPA derived SPMs. These novel immunoresolvents, their biosynthetic pathways and receptors have proven to promote resolution of inflammation, clearance of microbes, reduce pain and promote tissue regeneration via specific cellular and molecular mechanisms. As of July 20, 2020, PubMed.gov reports >1,150 publications for resolvins, confirming their potent protective actions from many laboratories worldwide. Since this field is rapidly expanding, we provide a short update of advances within 2–3 years from human and preclinical animal studies, together with the structural-functional elucidation of SPMs and identification of novel SPM receptors. These new discoveries indicate that SPMs, their pathways and receptors could provide a basis for new approaches to treating inflammation-associated diseases and to stimulating tissue regeneration via resolution pharmacology.

Introduction

Uncontrolled inflammation is now widely recognized as a critical component of many pathologies including cancer, arthritis, metabolic syndromes, chronic pain, periodontal, cardiovascular and neurological diseases, as well as bacterial and viral infections, such as

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COVID-19 (1–3). These are significant public health concerns, thus emphasizing the urgent need to understand the mechanisms controlling inflammation and its timely resolution, in order to develop new treatments (4–6). The acute inflammatory response is normally protective and self-limited, permitting repair of injured tissues and eliminating invading organisms, thus leading to complete resolution of leukocyte infiltrates and clearance of cellular debris and microbes enabling homeostasis (7). Although resolution of disease is appreciated by clinicians, it was considered a passive process (7), until we (2) and now many others (8, 9) obtained new evidence that resolution of self-limited inflammation is an active process. An early consensus report provided the definition and underscored the potential of this new field of resolution with impact in modern medicine and surgery (10).

Focusing on fundamental mechanisms in the resolution responses, the authors' laboratory uncovered several novel families of pro-resolving lipid mediators (LM) of inflammation that are biosynthesized from essential polyunsaturated fatty acid precursors, e.g. eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and n-3 docosapentaenoic (DPA). These potent bioactive molecules were named resolvins (Rv), protectins (PD), their aspirin-triggered (AT) isomers, and more recently maresins (MaR) as well as cysteinyl-conjugated SPMs (cys-SPMs), a superfamily collectively termed specialized pro-resolving mediators (SPMs). SPMs function as potent local resolution agonists, providing the first evidence that resolution is actively "turned on" and not simply a passive process. The complete structural elucidations of most SPMs are established (See Table 1 for the complete stereochemical names) and total organic synthesis achieved, which have enabled the confirmation of their potent bioactions and pro-resolving mechanisms at picomolar to low nanomolar concentrations in many cell types, and picogram to nanogram range in pre-clinical *in vivo* disease systems by researchers worldwide (2). Interested readers are directed to earlier reviews covering the original research (see 1, 2, 3, 10–12).

Current dogma and innovation:

The currently available pharmacopeia for treating inflammation consists mainly of inhibitors and receptor antagonists to manage hyper-inflammation and/or infectious inflammation, e.g. steroids, non-steroidal anti-inflammatory drugs (cyclooxygenase inhibitors) and the biologics that act by blocking cytokines such as anti-TNF therapies (13). New approaches are still needed to minimize or eliminate unwanted side effects and immune suppression that can accompany prolonged use of these traditional anti-inflammatory therapies. This is most evident in the need to control the cytokine storms and unexpected coagulopathies in COVID-19 patients (3, 14, 15). The emergence of new concepts and novel mediators within the resolution terrain that activate resolution and promote tissue regeneration have given rise to the new field of resolution pharmacology. These are subjects of several in-depth reviews that interested readers are directed to (2, 11, 16–19).

SPM production in humans

(I) SPM production in diseases and on challenge—While the structural elucidation of SPMs used mass spectrometry and other physical and bioactive properties, their production in humans is documented using targeted mass spectrometry-based LM metabololipidomics in many tissues and organs under physiologic and pathologic

conditions, and now by many other investigators (Table 2; reviewed earlier in (2, 12)). In several recent human trials, supplementation with omega-3 or marine oil increases select SPMs that correlate with enhanced phagocyte functions (Table 3; ref. (20); reviewed in (2)). SPM biosynthesis is impaired in several diseases, including tuberculous meningitis (21), multiple sclerosis (22), and osteoarthritis (23), suggesting that impaired endogenous resolution pathways might be a pathological etiology in these diseases. The biosynthesis of cys-SPMs and their complete stereochemistry are documented in human tissues, including brain, spleen, lymph nodes and bone marrow (24, 25), as well as in human platelets and macrophages exposed to pathogens (26). For n-3 DPA-derived SPMs in human, 13-series resolvins (RvTs) are increased following strenuous exercise, and $RvD_{n\text{-}3\ DPA}$ are regulated in a diurnal manner (27, 28).

In human challenge using a model of UV-killed *E. coli*-triggered skin inflammation, SPMs are biosynthesized locally at the start of resolution, including LXB_4, RvE1, RvD2 and AT-RvD1 (~10 pg/blister). This SPM panel, when given back to skin blisters at the concentrations present within blisters, reduces PMN numbers (29). Alsoin this human model, a synthetic cannabinoid anabasum, given orally as a CB2 agonist, increases RvD1 and RvD3, while reduces proinflammatory leukotriene (LT) B_4 and PMN infiltration, demonstrating pro-resolving actions of anabasum (30). With young adults taking ω-3 supplements, LC-MS-MS-based metabololipidomic profiling was verified in two separate laboratories with coded samples for inter-laboratory validation using human plasma and serum and low-dose intravenous lipopolysaccharide (LPS) challenge (31). Results from these laboratories with the same samples gave evidence in humans for temporal production of SPMs, supporting the role of SPMs in inflammation-resolution. Human neutrophils from individuals with metabolic syndrome following weight loss gave increased RvE1 production upon stimulation (32). Also, the human vagus nerve produces SPMs, e.g., RvE1, NPD1/PD1, MaR1, upon electrical stimulation (33) suggesting that this vagus-SPM circuit contributes to a new proresolving vagal reflex and reduction of leukotrienes (LT) and prostaglandins (PG) produced by the vagus nerve.

(II) Lipid mediator class switching and cell type-dependent SPM production—Temporal analyses of LM in experimental exudates indicate early appearance of LT and PG, followed by lipoxin (LX) biosynthesis, which was concurrent with resolution (reviewed in 4). Following these original findings in vivo and with human PMN (4), it was recently reported that *E. coli* and *S. aureus* each stimulate predominantly proinflammatory LTB_4 and PGE_2 in M1-macrophages, while stimulating M2-macrophages (34, 35). Also in human macrophages, high-mobility group box 1 protein (HMGB1) stimulates LT, while HMGB1 plus C1q switch macrophages to produce SPMs, including RvDs (36). Along these lines, a dual inhibitor of 5-LOX and microsomal prostaglandin E_2 synthase-1 selectively reduces LT and PG in M1, while enhancing SPMs (i.e. resolvins and maresins) in M2-macrophages (37). These results indicate that M1- and M2-like macrophages respond to pathogenic bacteria and pharmacologic inhibitors differently, biosynthesizing distinct LM profiles that further distinguish inflammatory versus pro-resolving phenotypes of these cells.

(III) Impact of age, sex and race on SPM production—Aging is associated with an overt inflammatory phenotype and physiological decline. In aged mice, resolution of inflammation is delayed and SPM levels reduced (38). Of interest, nano-proresolving medicines carrying SPMs reduce inflammation by promoting efferocytosis, providing evidence for age-dependent resolution pathways and novel means to activate resolution (38). In acute myocardial infarction, RvE1 is significantly lower in Black compared to White patients. In this study, PD1 is lower in White males compared to White female and Black patients (39). The prevalence of coronary heart disease is similar between Black and White patients, but cardiovascular events (including MI), rehospitalization, and mortality are disproportionately higher in Black patients. Whether lower RvE1 is associated with higher cardiovascular events and mortality in Black patients remains of interest. These findings emphasize the importance of assessing the age-, sex- and race-specific LM-SPM profiles in health and disease, in order to develop personalized and precision medicine. Moreover, these are areas of current ongoing research that shall yield important insights.

SPM functions in vitro and in vivo

(I) E-series Resolvins—Resolvin E1 was the first identified SPM derived from EPA (40), isolated from resolving exudates and disease models (Table 4) that reduced PMN infiltration (reviewed in 2), e.g. in carotid artery thrombosis upon fish oil and aspirin supplementation (41). In animal models of inflammatory diseases, RvE1 displays potent actions protecting against leukocyte-mediated tissue injury and excessive pro-inflammatory responses (reviewed earlier in (4)). RvE1 via its receptor ERV1/ChemR23 (Figures 1 & 2; reviewed in (42)) controls vascular inflammation, protecting against atherosclerosis by modifying oxidized LDL uptake and enhancing macrophage phagocytosis (43). In aortic valve stenosis, targeted deletion of ChemR23 in mice heightens disease progression (44). RvE1 also reduces neuroinflammation in a murine model of Alzheimer's disease (45), attenuates murine psoriatic dermatitis (46) and promotes intestinal epithelial wound healing in colitis (47). RvE1 also reduces tumor burden and enhances clearance of tumor cell debris (48). Since certain chemotherapeutic agents, e.g. cisplatin, trigger formation of tumor cell debris that stimulates growth of living tumor cells (48), SPMs provide a new therapeutic target that may be used in combination with chemotherapy to reduce cytotoxicity.

Current members of the E-series resolvins include RvE1, RvE2 and RvE3, with the recent addition and elucidation of RvE4 (49). RvE2 stops zymosan-induced PMN infiltration in murine peritonitis (50). RvE3 attenuates depression-like behavior in mice and airway allergic inflammation via IL23-IL17A pathway (51–53). RvE4, identified in physiologic hypoxia condition with M2-macrophages, stimulates efferocytosis of senescent erythrocytes *in vitro* and reduces mouse hemorrhagic exudates *in vivo* (49). Collectively, these results demonstrate tissue/organ-and cell type-specific actions of E-series resolvins in controlling acute and chronic inflammation, neurological disorders, cancer as well as stimulating tissue repair (Figure 3).

(II) D-series Resolvins—Using the mediator lipidomics-informatics approach, several bioactive compounds derived from DHA were isolated and identified, including both 17R alcohol-containing resolvins (17R-RvDs or AT-RvDs; via aspirin and COX-2 initiated

mechanisms (54)) and 17S alcohol-containing resolvins (RvDs; via LOX-initiated mechanisms (55); see Figure 1). Aspirin acetylates COX-2 to produce17R-alcohol-containing intermediate 17R-H(p)DHA that is converted by 5-LOX to produce 17R-isomers of RvDs (ref. (54); Figure 1). In addition to aspirin, N-acetyl sphingosine (N-AS), generated from acetyl-CoA and sphingosine via sphingosine kinase1 (SphK1), also acetylates COX2 and increases RvE1 and 17R-RvD1 (56).

(a) Resolvin D1 and 17R-resolvin D1: Both RvD1 and 17R-RvD1 are potent regulators of human and murine phagocytes at picomolar to low nanomolar concentrations (54, 55). They stimulate macrophage phagocytosis of microbes, efferocytosis of apoptotic PMN and tumor cell debris (57) as well as enhance efferocytosis in aging (58). In obesity-associated osteoarthritis, intra-articular treatment with RvD1 diminishes the progression of osteoarthritis in the knee joint (59). In a rat model of Parkinson's disease, RvD1 prevents central and peripheral inflammation (Table 4), as well as neuronal dysfunction and motor deficits (60). In a sickle cell disease mouse model, 17R-RvD1 promotes efferocytosis of PMN and erythrocytes (61). Also, 17R-RvD1 restores TLR9-impaired PMN phagocytosis and accelerates resolution of bacterial DNA-induced lung inflammation (62). Further, RvD1 promotes clearance of necroptotic cells by activating CDC42-dependent "eat-me signals" (63). RvD1 controls macrophage polarization; it increases pro-resolving markers such as arginase 1 and mannose receptor C-type 1, inhibiting tumor-associated macrophage (TAM), and regulates cardiac fibroblast plasticity (64, 65). RvD1 also induces a pro-revascularization phenotype in macrophages during tissue ischemia *via* its receptor, ALX/FPR2, that enhances tissue perfusion (66). In ischemia-reperfusion kidney injury, RvD1 increases Treg population via ALX/FPR2 pathways (67). Thus, RvD1 and 17R-RvD1 regulate leukocyte functions and plasticity, via activating their receptors ALX/FPR2 and DRV1/GPR32; see Figure 2 and for review (42).

(b) Resolvin D2: RvD2 is a potent regulator of bacterial sepsis (nanogram quantities) via its receptor DRV2/GPR18 in mice (Figure 2). RvD2 suppresses tumor growth and enhances clearance of tumor cell debris, while DRV2/GPR18-deficient mice display defective tumor clearance (48). Along these lines, the higher percentages of GPR18-positive PMN are associated with lower mortality in human sepsis (68). In several types of human cancers, GPR18 expression levels on tumor-infiltrating B lymphocytes are prognostic in that higher GPR18 levels are associated with higher percentages of overall survival (69). Both RvD1 and RvD2 are tissue/organ protective; RvD2 promotes keratinocyte repair in DRV2-dependent manner (70) and stimulates muscle regeneration (71), as well as limits tissue necrosis in burn wound (72). In periapical lesion of periodontitis, RvD2 increases DRV2 expression, and enhances pulp-like tissue regeneration and healing of periapical lesion (73). With conjunctival goblet cells, RvD2 stimulates mucin secretion via elevated cAMP (74). Thus, in addition to its potent actions on phagocytes, RvD2 displays cell type-and organ-specific actions promoting tissue protection, repair and regeneration.

(c) Resolvin D3 and 17R-resolvin D3: Both RvD3 and 17R-RvD3 potently regulate leukocyte-directed actions in vitro and in vivo ((75); reviewed in (25)). In lung epithelial cells, RvD3 increases NF-κB counter-regulators (76). RvD3 and 17-RvD3 both display anti-

cancer activity in murine systems (57, 77), raising the possibility of targeting and stimulating resolution pathways for treatment of cancer.

(d) Resolvin D4: Several different total organic syntheses of RvD4 were achieved. The first total synthesis of RvD4 established its stereochemical configuration, which permits uncovering RvD4's ability to clear *S. aureus* skin infections and stimulate efferocytosis by dermal fibroblasts (78). A second stereoselective synthesis of RvD4 was reported (79). And recently, RvD4 was scaled-up in a new commercial synthesis, and this synthetic RvD4 displays organ protection in two mouse ischemic injury models (80). In a murine model of deep vein thrombosis, RvD4 reduces thrombus burden and decreases the release of neutrophil extracellular traps (NETs), i.e. NETosis, a critical component for thrombosis (Figure 4) development (81). These findings and new roles of RvD4 suggest that SPMs could provide an effective strategy in controlling thrombo-inflammatory disease.

(e) Resolvin D5: RvD5 controls *E. coli* and *S aureus* infection, lowering antibiotic requirements for bacterial clearance (82). With human cells, RvD5 stimulates phagocytosis of *E. coli* by both M1- and M2-like human macrophages (35). Of interest, RvD5 is the first SPM that shows sex dimorphism in pain regulation, inhibiting both neuropathic and inflammatory pain in male but not with female mice (83).

(III) Protectins—Protectin D1/Neuroprotectin D1 is biosynthesized from DHA via 15-LOX-initiated mechanism in several human cell types, murine exudates, and brain tissues (55). Establishment of its complete stereochemical assignments ((84) and reviewed in (12)) enabled the demonstration of its potent actions in many disease systems. When of neural origin, NPD1 is used, and PD1 is used to denote its peripheral actions. PD1/NPD1 displays potent neuroprotective actions in brain, retina and central nervous system, e.g. protecting from ischemic stroke, retina degenerative disease (reviewed in 12) and traumatic brain injury (85). The aspirin-triggered epimer 17R-NPD1 shares the action of NPD1 in controlling PMN, enhancing macrophage functions and attenuating experimental stroke (86, 87).

(IV) Maresins—The *Ma*crophage mediator in *re*solving *in*flammation, denoted maresins (MaR), were first identified in human macrophages (MΦ) via 12-LOX-initiated mechanisms (88). Next, the complete stereochemistry of maresin 1 (MaR1) was determined, its total organic synthesis was achieved and confirmed by several independent teams (reviewed in 12). We investigated MaR1's ability in stimulating tissue regeneration using a freshwater flatworm, namely planaria, as a primordial model organism, since it possesses robust regenerative capability. The stereochemically defined synthetic MaR1 accelerates planaria regeneration following head resection, reduces pain and is neuroprotective (12). MaR1 is also biosynthesized during platelet-PMN interactions (25), and MaR1, RvD2 and RvD1 each reduce cold-stored platelet activation (89), which may be important for long-term cold platelet storage needed for transfusion. Recently,MaR1 was found to improve functional neurological recovery after spinal cord injury (90), attenuate neuroinflammation in perioperative neurocognitive disorders in mice (91), as well as reduce mechanical and thermal hyperalgesia (i.e. enhanced pain sensitivity) (92). Following tooth extractions, MaR1 reduces post-operative pain, accelerates wound healing and promotes socket bone

regeneration (93). In skin, MaR1 reduces psoriasis-like inflammation and UVB irradiation damage (94, 95). Thus, MaR1 is pro-regenerative, pro-repair and neuroprotective in a wide range of tissues and organs across phyla. MaR1 activates two different classes of receptors, namely leucine-rich repeat-containing G protein–coupled receptor 6 (LGR6), a cell surface G protein-coupled receptor on phagocytes (96), and retinoic acid-related orphan receptor α (ROR-α), a nuclear receptor on liver macrophages that might be relevant in liver pathology (97). These findings highlight the cell-type specific and receptor-dependent actions of MaR1.

(V) Cysteinyl SPMs (cys-SPMs)—Three new series of peptide-lipid conjugated SPMs were recently identified, including maresin conjugates in tissue regeneration (MCTR), protectin conjugates in tissue regeneration (PCTR) and resolvin conjugates in tissue regeneration (RCTR), collectively coined cysteinyl-SPMs (cys-SPMs) (98) (reviewed in 25). Each series contains 3 bioactive members that display potent (picogram to nanogram range) pro-regenerative and pro-repair actions, including stimulating regeneration of freshwater planaria and promoting tissue repair in acute lung injury (24, 98). In addition, MCTRs exhibit cardiovascular protection in mice and in primordial sea squirt, as well as counter LTD_4-initiated signals and vascular response (99). In murine allergic airway inflammation, MCTRs block LTD_4-induced airway contraction (100, 101). MCTR1 and PCTR1 also prevent LPS-induced acute respiratory distress syndrome and multiple organ damage (102, 103). Thus, the organ-protective actions of cys-SPMs are evolutionarily conserved across phyla, from primordial lower-phylum species such as planaria and sea squirt to mice and humans.

(VI) n-3 DPA-derived SPMs—In addition to EPA and DHA, n-3 DPA is also converted to novel SPMs, including $RvD_{n\text{-}3\ DPA}$, $MaR_{n\text{-}3\ DPA}$ and $PD_{n\text{-}3\ DPA}$, as well as 13-series resolvins (RvTs) (28, 104). Biosynthesis of RvTs is increased by atorvastatin via S-nitrosylation of COX-2 during neutrophil-endothelial cell interactions. RvTs and atorvastatin demonstrate additive protection, increasing survival during *E. coli* infections (28). Stereochemistries of some of the n-3 DPA-derived SPMs are established using total organic synthesis (105, 106). Using the synthetic authentic compounds, these n-3 DPA-derived SPMs share the potent protective actions of the EPA-and DHA-derived SPMs in regulating key innate protective responses, dampening GI, joint, cardiovascular and neuroinflammation as well as promoting timely resolution (27, 107–110).

SPM Receptors and mimetics

SPMs stimulate resolution via activating cell surface GPCRs. Each SPM demonstrates stereoselective activation of its own specific GPCR, leading to some overlapping downstream signals, pathways and pro-resolving functions. The affinities of SPMs for their respective GPCRs (i.e. Kd values) are in the low nanomolar range, consistent with their bioactions *in vitro* and *in vivo*. Deficit of ALX/FPR2, a RvD1 receptor, in mice amplifies leukocyte-directed endothelial dysfunction, cardiomyopathy and age-related obesity (111). See Figures 2 and 3, and recent reviews (42, 112) for details on mechanisms and roles in cardiovascular pathologies.

(I) Newly discovered SPM receptors—Several new SPM receptors were recently uncovered. NPD1/PD1 activates GPR37, increasing intracellular Ca^{2+} and phagocytosis with macrophages. Mice lacking *Gpr37* display defects in macrophage phagocytic activity and delayed resolution of inflammatory pain (113). Using an unbiased screening of > 200 GPCRs, MaR1 was identified as a stereoselective activator for human leucine-rich repeat containing G protein-coupled receptor 6 (LGR6), expressed in phagocytes. MaR1-specific binding to LGR6 was confirmed using ^{3}H-labeled MaR1. With human and mouse phagocytes, MaR1 stimulates phagocytosis, efferocytosis, and phosphorylation of select proteins in a LGR6-dependent manner. MaR1 is therefore an endogenous activator of human LGR6, stimulating MaR1's key proresolving functions of phagocytes (96). The first GPCR for n-3 DPA-derived resolvins was recently identified. Using a similar GPCR screening approach and radioactive ligand, $RvD5_{n\text{-}3\ DPA}$ was shown to bind to an orphan receptor GPR101 with high selectivity and stereospecificity, as well as RvD5. Knockdown of GPR101 *in vivo* reverses the protective actions of $RvD5_{n\text{-}3\ DPA}$ in limiting joint and gut inflammation during inflammatory arthritis (114). Taken together, these newly identified SPM receptors together with ALX/FPR2, ERV1/ChemR23, DRV1/GPR32 and DRV2/GPR18 display potent pro-resolving properties with ligand-receptor specificity, as evidenced by structure-function activity (SAR) established for each receptor. In addition, receptor activation by each SPM initiates overlapping (e.g. cAMP signal for ALX with calcium mobilization, GPR18, LGR6 and GPR101) and distinct signals (e.g. intracellular [Ca^{2+}] for PD1) on phagocytes, likely acting in tandem to govern host defense against injury, inflammation and infection to ensure timely resolution.

(II) SPM Mimetics—SPMs are subject to rapid further metabolism via enzymatic inactivation (Figure 1). Metabolically stable analogs that resist enzymatic inactivation were designed and synthesized (115), and new benzo-diacetylenic 17R-RvD1 methyl ester (BDA-RvD1) mimetic with reduced chiral centers and steps in organic synthesis shares defining pro-resolving actions with RvD1 (116). Using a high-throughput screening of small-molecule libraries (>48,000 compounds), several chemotypes were identified to activate recombinant DRV1 and stimulate macrophage phagocytosis of live *E. coli* in DRV1-dependent manner (117). These molecules act as RvD1 mimetics, offering templates for potentially more cost-effective synthesis to facilitate clinical development of therapeutics that stimulate resolution pathways. Also, a benzo-RvE2 analog was prepared, showing amazing femtomolar potency in reducing inflammation *in vivo* (118).

SPMs control infections

Select SPMs exhibit potent host-protective actions in bacterial, parasite and viral infections (2, 5). The anti-inflammatory and pro-resolving actions of SPMs were proven. Their ability to clear live microbes was unexpected. We first uncovered resolvins' ability to enhance bacterial killing and clearance while maintaining limited collateral tissue damage (82); these unanticipated actions of resolvins opened the study of SPMs in microbial control.

(I) Bacterial infection—In a microbial sepsis, SPMs display multi-level mechanisms, controlling excessive inflammatory responses, reducing bacterial loads and increasing survival (25). In *E. coli* and *S. aureus* murine infections, RvDs and PD1 reduce pro-

inflammatory cytokines IL-1beta and IL-6, while increasing anti-inflammatory IL-10 and interferon (IFN)-gamma (82). Select cys-SPMs also accelerate resolution of *E. coli* infection, shortening resolution intervals (2, 24). Also, RvD1 and MaR1 control *M. tuberculosis* infection, increasing expression of antibacterial peptides (119). In *P. aeruginosa* lung infection, RvD1 reduces lung bacterial load, inflammation, and tissue damage relevant in cystic fibrosis patients (120).

(II) Parasitic infection—Chagas disease, transmitted by a protozoan named *Trypanosoma cruzi*, is a major public health issue worldwide. From patients with Chagas disease, 17R-RvD1 significantly reduces *T. cruzi* antigen-stimulated PBMC proliferation (121), and RvD1 in a murine model of *T. cruzi* infection increases survival, controls parasite replication and prevents cardiac fibrosis (122).

(III) Viral infection—In a murine model of stromal keratitis (SK), a common cause of blindness caused by herpes simplex virus (HSV)-1 infection, RvE1 and AT-RvD1 reduce HSV-1 ocular infection (42). In lethal influenza H5N1 virus infection, a PD1 isomer protects mice via inhibiting viral replication (123). Also, 17-HDHA, a pathway marker and precursor to D-series Rvs, enhances the antibody-mediated immune response against influenza virus H1N1, exhibiting an adjuvant-like property (124). In viral and bacterial coinfection (pneumonia with *Streptococcus pneumoniae* and influenza A virus), 17R-RvD1 significantly reduces neutrophil elastase (NE) activity, while accelerating clearance of pneumococci in the lungs (125). Thus, 17R-RvD1 could be harnessed for the treatment of chronic obstructive pulmonary disease and other diseases that impact lungs such as COVID-19 and cystic fibrosis that are typically complicated by both viral and bacterial respiratory pathogens.

(IV) SPMs and SARS-CoV-2 infection—Severe acute respiratory syndrome (SARS) is a viral respiratory illness caused by a single-stranded RNA virus, namely SARS-associated coronavirus (SARS-CoV), reported in 2003. The current Coronavirus Disease 2019 (COVID-19) pandemic is caused by a new strain SARS-CoV-2 (https://www.cdc.gov/sars/index.html). In light of COVID-19 pathologies with inflammation of the respiratory and cardiovascular systems (126–131), anti-inflammatory, pro-resolving, microbial clearance and organ-protective actions of SPMs may be useful in controlling disease severity. These include:

a. *Hyper-inflammation*; SARS-CoV-2 infection is associated with hyper-inflammatory status, including excessive inflammatory cell infiltration, inflammasome activation and the “cytokine storms” (131). Intravenous administration of fish oil emulsions has been proposed as a parenteral supplementation for critically ill COVID-19 patients, because the high content of EPA and DHA (precursors of SPMs) could help to reduce cytokine storms (132, 133). In this context, SPMs limit neutrophil infiltration and reduce pro-inflammatory cytokines in lungs and other organs during bacterial and viral infections (38; see “bacterial infection” above). In addition, select SPM including RvTs, RvD2 and MaR1 block inflammasome components leading to reduced IL-1b release (28, 134, 135). Thus, SPM may be useful in controlling cytokine storms in COVID-19 patients as proposed in (3, 14).

b. *NETs, venous thrombosis and hypercoagulation*; aberrant NETosis, i.e. the process of neutrophil extracellular trap (NET) formation (Figure 4), is observed in many patients with COVID-19, which may lead to acute respiratory distress syndrome (ARDS) (126, 130). As demonstrated in deep vein thrombosis model, RvD1, RvD4 and MaR1 reduce venous thrombus burden and RvD4 decreases the release of NETs, i.e. NETosis (81). Also, RvD1 inhibits markers of NETosis in a murine model of aortic aneurysm (136). RvE4 stimulates efferocytosis of senescent erythrocytes in hemorrhagic exudates in hypoxic conditions (49), such as those in COVID-19 patients (137).

c. *ARDS*; the pathology of ARDS has been associated with severe COVID-19 patients, possibly triggered by NETosis and cytokine storm (126–128). In this regard, SPMs are potent regulators of acute lung injury including ARDS, reducing leukocyte accumulation in lungs and protecting from lung damage (138).

d. *Neurological disorder*; COVID-19 can cause neurological disorders, including stroke, blood-brain barrier disruption, and endothelial cell damage in the brain (129). In this regard, NPD1 and 17R-NPD1 protect from ischemic stroke (12, 86, 87); RvD1 and PD1 attenuate inflammation-induced blood-brain barrier dysfunction (22).

LM including SPMs were identified in serums from COVID-19 patients (139). There is distinct separation between SPMs and prostanoids (prostaglandins and thromboxane), and SPMs change during disease courses. For example, RvE3 is reduced in severe compared to moderate COVID-19 patients (139). Treatment of COVID-19 patients with dexamethasone lowered 28-day mortality among those who received respiratory support (140). Along these lines, in murine allergic airway inflammation, dexamethasone increases SPMs, particularly protectins (141). Therefore, it is possible that targeting SPM pathways and metabolomes (Figure 1) could provide a novel therapeutic approach for treating SARS-CoV-2 infections (Table 4).

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Summary Points

- Resolution of inflammation is an active biosynthetic process that connects the first response of the innate immune system to biosynthesis of the specialized proresolving mediators (SPMs) including resolvins, protectins and maresins, as well as novel cys-SPMs.
- Mass spectrometry-based profiling approaches for the resolution metabolome have documented the temporal production of SPMs in humans and preclinical animal systems. Today, hundreds of independent investigators confirm and extend the potent actions of each of the SPM pathway bioactive metabolomes (e.g. resolvins, maresins, lipoxins, (neuro)protectins and cys-SPMs).
- SPMs evoke proresolving responses via activating their G protein-coupled receptors and downstream intracellular mechanisms in the concentrations at which they are produced locally.
- The structural elucidation and complete stereochemical assignments of each SPM enable confirmation of their potent actions in controlling inflammatory response, promoting resolution and tissue repair, thus opening the opportunity for studying resolution physiology and pharmacology.
- The goal of resolution pharmacology is to stimulate the host innate response to accelerate microbial clearance, limit collateral tissue damage and stimulate tissue regeneration. This might be achieved in part via personalized profiling of resolution metabolomes and following specific SPM treatment to provide precision medicine and nutrition support.

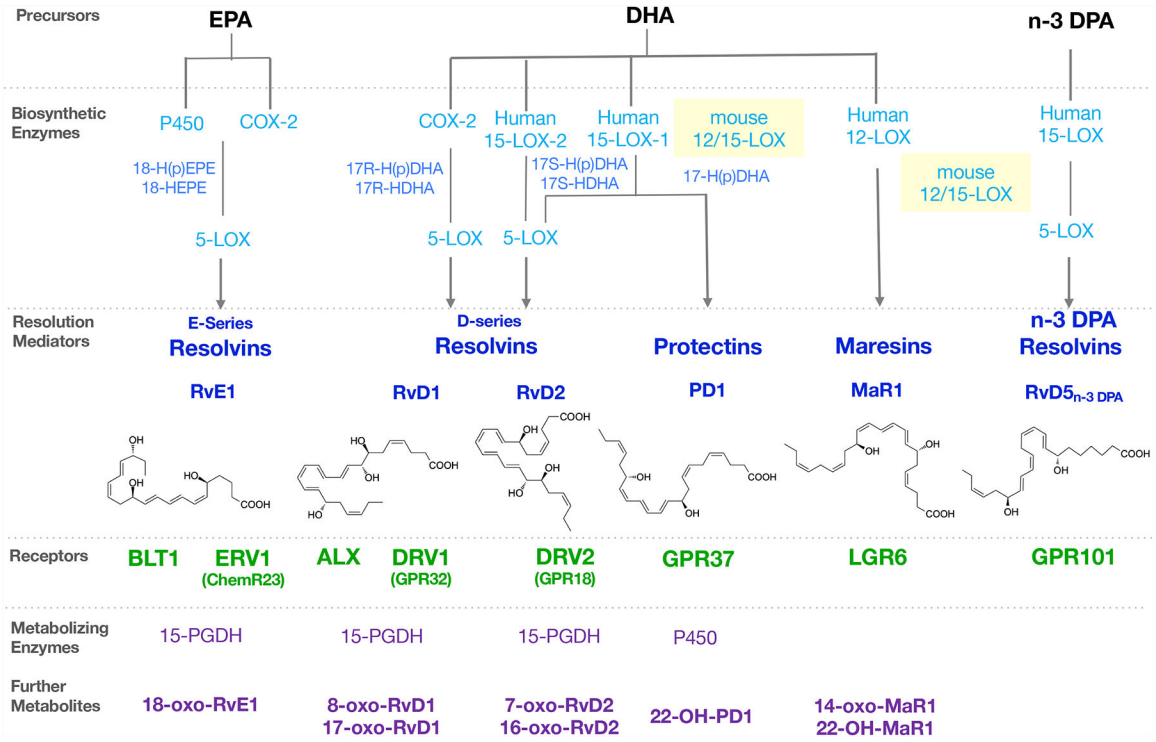

Figure 1. Illustration of resolution metabolome: SPM biosynthesis, receptors and inactivation

Precursors EPA, DHA and n-3 DPA are converted via biosynthetic enzymes to SPMs, which activate their specific receptors to stimulate pro-resolving immune functions. The SPMs are rapidly enzymatically converted to metabolites with diminished or reduced activity.

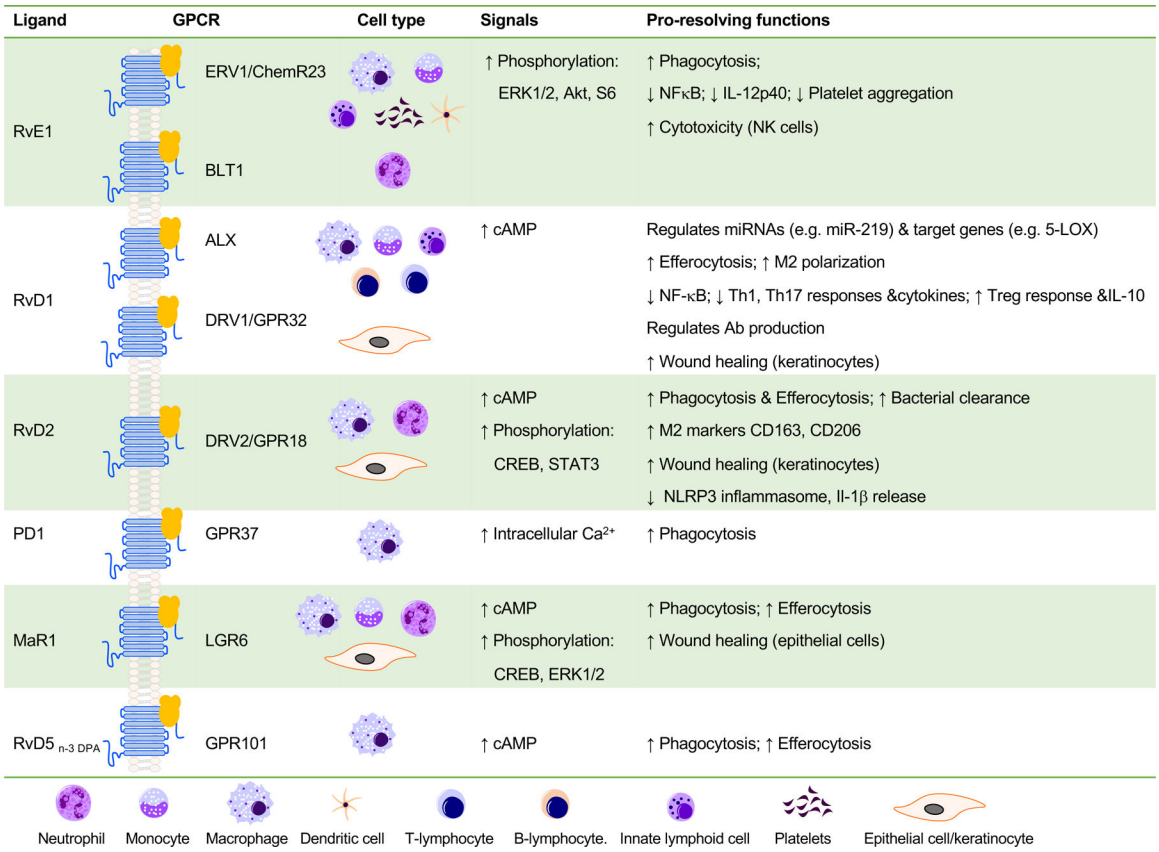

Figure 2. SPM receptor networks

SPMs stimulate resolution via activating cell surface GPCRs. RvE1 activates ERV1/ChemR23, leading to phosphorylation of Akt/S6 protein pathways that stimulates macrophage phagocytosis. RvD1 activates both DRV1/GPR32 and ALX, leading to regulation of microRNAs and their target genes, increases of efferocytosis (macrophage phagocytosis of apoptotic PMN) and M2 macrophage polarization. RvD2 activates GPR18, leading to cAMP release and phosphorylation of select kinases and transcription factors, essential for macrophage phagocytosis. Besides phagocytes, SPMs also display cell type-specific actions. For example, RvE1 activates both ERV1/ChemR23 and BLT1 on human conjunctival goblet cells to stimulate mucin secretion (158). 17R-RvD1 attenuates vascular smooth muscle cell migration via ALX/FPR2 and cAMP/PKA activity (159). RvD2-GPR18 axis enhances wound repair with human on keratinocytes (70). See text and earlier reviews (42, 112) for further details.

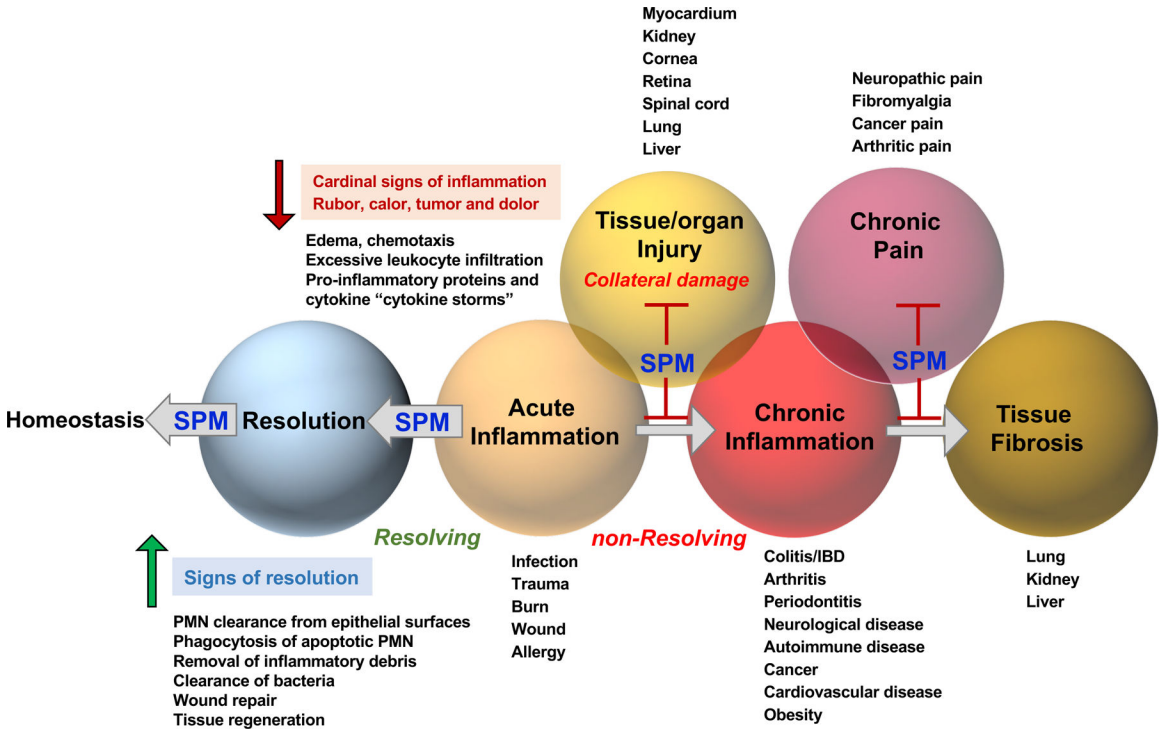

Figure 3. Temporal phases in inflammation-resolution and SPM actions in preclinical animal disease models.

In *in vivo* animal diseases, select SPMs not only control classic non-resolving inflammation conditions, but also reduce collateral damages such as tissue and organ injuries, chronic pain and tissue fibrosis. They are normally active in picogram to low nanogram quantities, that is 100–1000x more potent than widely used classic NSAID. In the case of controlling pain, RvE1 is 1000X more potent than morphine (160). As potent agonists *i.e.* immunoresolvents, SPMs promote resolution and homeostasis via limiting excessive inflammatory responses (e.g. limiting PMN infiltration and cytokine storm), and enhancing efferocytosis, bacterial clearance, wound repair as well as tissue regeneration, defining the signs of resolution.

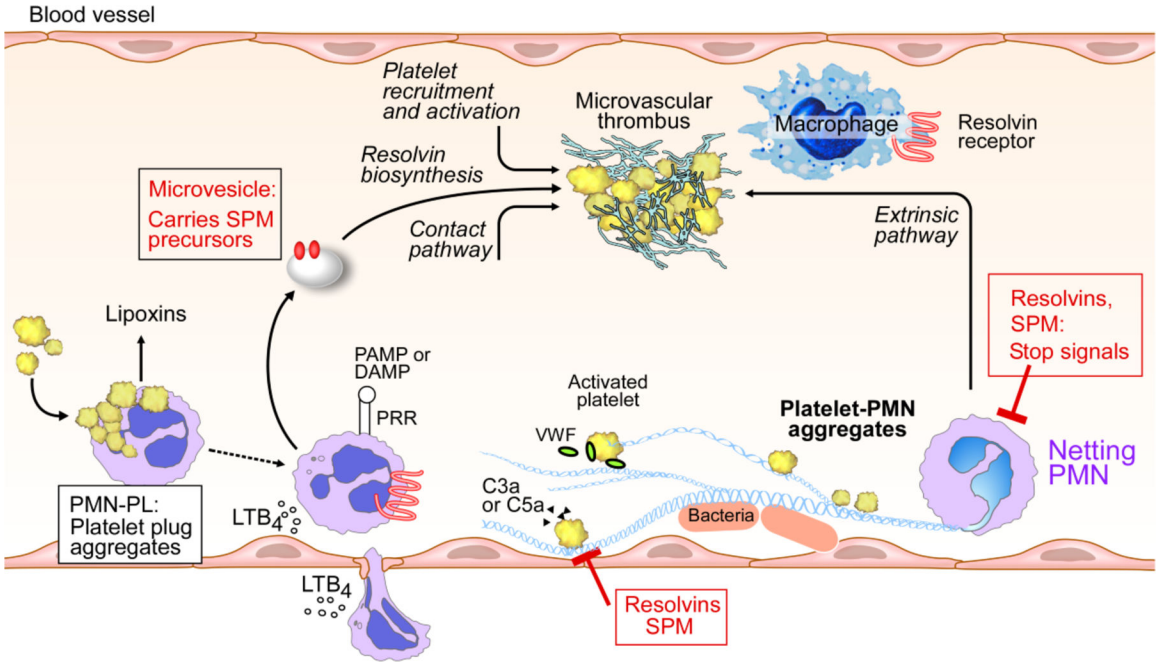

Figure 4. Microvascular thrombosis and the roles of SPMs

Illustration of the intraluminal production and action of SPMs; PMN-platelet interactions initiate production of lipoxins and other SPMs, e.g. MaR1 (reviewed in 4). Microvesicles released from PMN also contribute to SPM formation (reviewed in 25). Select SPMs including LXA_4, MaR1, RvD1 and RvD4 enhance thrombus resolution, and RvD4 reduces NETosis (81).

Table 1.

SPMs and cys-SPMs: Stereochemical names and assignments

Substrate	SPM	Chemical name	PubChem**** CID:	Lipid Maps***** LM_ID
EPA	*E-series Resolvins			
	RvE1	5*S*,12*R*,18*R*-trihydroxy-6*Z*,8*E*,10*E*,14*Z*,16*E*-eicosapentaenoic acid	10473088	LMFA03140003
	RvE2	5S,18R-dihydroxy-6E,8Z,11Z,14Z,16E-eicosapentaenoic acid	16061125	LMFA03140011
	RvE3	17*R*,18*R*-dihydroxy-5*Z*,8*Z*,11*Z*,13*E*,15*E*-eicosapentaenoic acid	60150429	LMFA03140006
	RvE4	5*S*,15*S*-dihydroxy-6E,8Z,11Z,13E,17Z-eicosapentaenoic acid		
DHA	**D-series Resolvins			
	RvD1	7*S*,8*R*,17*S*-trihydroxy-4*Z*,9*E*,11*E*,13*Z*,15*E*,19*Z*-docosahexaenoic acid	44251266	LMFA04030011
	RvD2	7S,16R,17S-trihydroxy-4Z,8E,10Z,12E,14E,19Z-docosahexaenoic acid	11383310	LMFA04030001
	RvD3	4S,11R,17S-trihydroxy-5Z,7E,9E,13Z,15E,19Z-docosahexaenoic acid	71665428	LMFA04030012
	RvD4	4S,5R,17S-trihydroxydocosa-6E,8E,10Z,13Z,15E,19Z hexaenoic acid	16061138	LMFA04030002
	RvD5	7S,17S-dihydroxy-4Z,8E,10Z,13Z,15Z,19E-docosahexaenoic acid	16061139	LMFA04030003
	RvD6	4S,17S-dihydroxy-5E,7E,10Z,13Z,15E,19Z-docosahexaenoic acid	25073193	LMFA04030004
	Protectins			
	NPD1/PD1	10R,17S-dihydroxy-4Z,7Z,11E,13E,15Z,19Z-docosahexaenoic acid	16042541	LMFA04040001
	Maresins			
	MaR1	7R,14S-dihydroxy-4Z,8E,10E,12Z,16Z,19Z-docosahexaenoic acid	60201795	LMFA04050001
	MaR2	13R,14S-dihydroxy-4Z,7Z,9E,11E,16Z,19Z-docosahexaenoic acid	101894912	LMFA04050004
	eMaR	13S,14S-epoxy-docosa-4Z,7Z,9E,11E,16Z,19Z-hexaenoic acid	72204813	LMFA04050002
	Cysteinyl SPMs			
	MCTR1	13R-glutathionyl-14S-hydroxy-4Z,7Z,9E,11E,16Z,19Z-docosahexaenoic acid	122368871	
	MCTR2	13R-cysteinylglycinyl-14S-hydroxy-4Z,7Z,9E,11E,16Z,19Z-docosahexaenoic acid	122368872	
	MCTR3	13R-cysteinyl-14S-hydroxy-4Z,7Z,9E,11E,16Z,19Z-docosahexaenoic acid	122368873	
	PCTR1	16R-glutathionyl-17S-hydroxy-4Z,7Z,10Z,12E,14E,19Z-docosahexaenoic acid	132472316	
	PCTR2	16R-cysteinylglycinyl-17S-hydroxy-4Z,7Z,10Z,12E,14E,19Z-docosahexaenoic acid	132472317	
	PCTR3	16R-cysteinyl-17S-hydroxy-4Z,7Z,10Z,12E,14E,19Z-docosahexaenoic acid	132472318	
	RCTR1	8R-glutathionyl-7S,17S-dihydroxy-4Z,9E,11E,13Z,15E,19Z-docosahexaenoic acid	132472320	

Substrate	SPM	Chemical name	PubChem**** CID:	Lipid Maps***** LM_ID
	RCTR2	8R-cysteinylglycinyl-7S,17S-dihydroxy-4Z,9E,11E,13Z,15E,19Z-docosahexaenoic acid	132472321	
	RCTR3	8R-cysteinyl-7S,17S-dihydroxy-4Z,9E,11E,13Z,15E,19Z-docosahexaenoic acid	132472322	
n-3 DPA	n-3 DPA-derived SPMs			
	RvD1 $_{\text{n-3 DPA}}$	7S,8R,17S-trihydroxy-9*E*,11*E*,13*Z*,15*E*,19Z-docosapentaenoic acid		
	RvD2 $_{\text{n-3 DPA}}$	7,16,17-trihydroxy-8,10,12,14,19-docosapentaenoic acid		
	RvD5 $_{\text{n-3 DPA}}$	7S,17S-dihydroxy-8E,10Z,13Z,15Z,19E-docosapentaenoic acid		
	PD1 $_{\text{n-3 DPA}}$	10R,17S-dihydroxy-7Z,11E,13E,15Z,19Z-docosapentaenoic acid		
	PD2 $_{\text{n-3 DPA}}$	16,17-dihydroxy-7Z,10,13,14,19-docosapentaenoic acid		
	MaR1 $_{\text{n-3 DPA}}$	7R,14S-dihydroxy-8E,10E,12Z,16Z,19Z-docosapentaenoic acid		
	MaR2 $_{\text{n-3 DPA}}$	13,14-dihydroxy-7,9,11,16,19-docosapentaenoic acid		
	MaR3 $_{\text{n-3 DPA}}$	14, 21-dihydroxy-7,10,12,16,19-docosapentaenoic acid		
	RvT1 ***	7S,13R,20S-trihydroxy-8E,10Z,14E,16Z,18E-docosapentaenoic acid	124202379	LMFA04000091
	RvT2	7,12,13-trihydroxy-8,10,14,16,19-docosapentaenoic acid	124202381	LMFA04000092
	RvT3	7,8,13-trihydroxy-9,11,14,16,19-docosapentaenoic acid	124202383	LMFA04000093
	RvT4 ***	7S,13R-dihydroxy-8E,10Z,14E,16Z,19Z-docosapentaenoic acid	124202385	LMFA04000094

The complete stereochemical assignments listed here were established in earlier publications from the authors' lab.

*18S-RvEs contain 18S-hydroxyl group; see (142);

**17R-RvDs contain 17R-hydroxyl group.

***See (143) for total synthesis of RvT1 and RvT4

****For 2D and 3D structure models of SPMs; see https://pubchem.ncbi.nlm.nih.gov/

*****https://www.lipidmaps.org/data/structure/LMSDSearch.php?Mode=SetupTextOntologySearch

Table 2.

SPM production in humans: Identification and quantification by mass spectrometry*

Tissue/organ	SPMs	Quantities	Reference
Serum (Tuberculosis and Type 2 diabetes)	RvE2,3, RvD1,2,4,5,6, PD1, 17R-PD1, MaR1,2, MCTR3, RvTs, $RvD_{n\text{-}3\ DPA}$, $PD1_{n\text{-}3\ DPA}$, $MaR1_{n\text{-}3\ DPA}$	range 0.2–28 pg/ml	(144)
Lymph nodes	MCTR1-3, PCTR1-3	1–5 pg/500 mg protein	(24)
Spleen	MCTR1, MCTR2, PCTR1, RCTR1-3	1–5 pg/500 mg protein 60–400 pg/500 mg protein	(24)
Brain	MCTRs, PCTRs, RCTRs	1–5 pg/500 mg protein	(24)
Plasma	$RvD_{n\text{-}3\ DPA}$	10–30 pg/ml	(27)
	RvEs, RvDs, PD1, MaR1 (Type 2 diabetes mellitus)	30–190 pg/ml	
Cerebrospinal fluid	RvT2, RvT4 (Tuberculous meningitis)	1–2 pg/ml	(21)
	RvD1, RvD5 PD1 (multiple sclerosis)	0.02–0.68 pg/ml	(22)
Synovial fluid	PD1, RvD1, RvD2, RvD5, MaR1 (RA and OA)	~5 pmol/ml	(23)
Bone marrow	RvD4		(80)
	MCTR1	6 pg/4 ml	(24)
	RCTR1-3	24–180 pg/4 ml	
Blister	RvEs, RvDs, PD1, MaR1 AT-RvD1	0.1–10 pg/blister	(29)
	RvD1, RvD3	10–15 pg/ml	(30)
Vagus nerve (electric stimulation)	RvE1-3, RvD3-6, NPD1/PD1, MaR1	1–40 pg/3.5 cm of tissue	(33)
Metabolic syndrome (weight loss program)	RvE1, RvE3, RvD2, MaR1 (neutrophils +A23187)	26–1340 pg/4.5 × 10^6 PMN	(32)
Obesity	RvD1-6, MaR1, MaR2, PD1, RvEs (Plasma and leukocytes)	0.2–200 pg/ml plasma, 0.1–2 pg/3×10^6 cells	(145)
Stenotic aortic valves	RvE1, RvD3	~500 – 3500 pg/g tissue	(44)
Sputum (cystic fibrosis)	RvD1	~200 pg/ml	(120)
SARS-CoV-2 infection	RvE3, RvD1-4, PD1		(139)

*Please see (2, 12) for earlier publications on human SPM production and text for further details.

Table 3.

Supplementation: Production and increase of SPMs

(A) Human trials				
Diseases/conditions	**Doses and regimen**	**SPMs present**	**SPMs that are increased by supplementation**	**Reference**
Chronic kidney disease	n-3 PUFA; 4 g/day; 8 wks	RvE1, RvE2, RvE3, RvD5 (plasma)	RvE1, RvE2, RvE3, RvD5	(146)
Effect of n-3 in pregnancy on offspring	n-3 PUFA ethyl esters with DHA (56.0%) and EPA (27.7 %); 3.7 g/day; from 20 wks gestation until delivery	18-HEPE, 17-HDHA RvE1, RvE2, RvE3, RvD1, 17R-RvD1, RvD2 (cord blood)	18-HEPE, 17-HDHA	(147)
Healthy individuals (Serum & plasma)	Study A - ω-3 triglyceride form; 900 mg/d (550 mg EPA and 350 mg dHa) or 1800 mg/d (1100 mg EPA and 700 mg DHA); 5 months Study B - 3.4 grams/d EPA and DHA (in the form of four capsules each containing 460 mg of EPA-ethyl ester and 380 mg of DHA-ethyl ester); 8–12 wks	RvE1, RvD1, 17=HDHA, 18-HEPE (plasma and serum)	RvE1, RvD1, 17=HDHA, 18-HEPE	(31)
Peripheral artery disease (OMEGA-PAD II trial)	n-3 PUFA; 325 mg EPA and 225 mg DHA per capsule; 4.4 g (4 capsules)/day; 3 months	RvE1, RvE2, RvE3 (plasma)	RvE3	(148)
Peripheral artery disease with marine oil supplementation	PUFA with EPA (≈46%), n-3 DPA (≈18%), and DHA (≈33%); 1.5, 3, and 4.5 g/day; 5 days	RvEs, RvDs, PD, MaR, MCTRs, PCTRs, RvTs, $RvD_{n\text{-}3\ DPA}$, $PD_{n\text{-}3\ DPA}$, $MaR_{n\text{-}3\ DPA}$ (plasma)	MaR	(149)
Healthy individuals (marine oil supplementation)	PUFA with EPA (≈46%), n-3 DPA (≈18%), and DHA (≈33%); 1.5, 3, and 4.5 g/day; 2 wks	RvEs, RvDs, PD1, MaR1, MCTRs, PCTRs, RvTs, $RvD_{n\text{-}3\ DPA}$, $PD_{n\text{-}3\ DPA}$, $MaR_{n\text{-}3\ DPA}$ (plasma)	RvEs, RvDs, PD1, MaR1, MCTRs, PCTRs, RvTs, $RvD_{n\text{-}3\ DPA}$, $PD_{n\text{-}3\ DPA}$, $MaR_{n\text{-}3\ DPA}$	(20)
Arthritis	Microalgae oil (Schizochytrium sp); 2.1 g DHA/day; 10 wks	14-HDHA, 17-HDHA (plasma)	14-HDHA, 17-HDHA	(150)
(B) Animal disease systems				
Diseases/conditions	**Doses and regimen**	**SPMs present**	**SPMs that are increased by supplementation**	**Reference**
Peritonitis and Sepsis (mouse)	omega-3 lipid emulsions; infusion ~2 mg/g/day; 24 hours	18-HEPE, MaR1, PDx	18-HEPE, MaR1, PDX	(151)
Liver (rat)	DHA; 300 mg/kg; 3 days;	RvE1, RvE2, RvD1, RvD2	RvD1, RvD2	(152)
	EPA; 50 mg/kg; 12 wks	RvE1, RvE2, RvD1, RvD2	RvE1, RvE2, RvD1, RvD2	(153)
Asthma (mouse)	Long-chain PUFA; 1g/kg EPA, 229.6 mg/kg DHA; 24 days	RvEs, RvDs, PD1, MaR2, MCTRs, PCTRs, RCTRs, RvTs, $RvD_{n\text{-}3\ DPA}$, $PD_{n\text{-}3\ DPA}$, $MaR_{n\text{-}3\ DPA}$ (lungs)	RvD1, RvD4	(154)
Brain (neonatal piglet)	Herring oil; 40 mg DHA/kg; 10 days	RvD1		(155)

Table 4.

Updates on SPM actions in animal models of diseases from recent 3 years

Diseases/conditions	SPMs that resolve inflammation and reduce disease severity	Reference
Infection	Bacterial: MCTRs, PCTR1, RCTRs	(24, 25)
	$RvD5_{n\text{-}3\ DPA}$	(114)
	Viral: 17R-RvD1	(125)
Acute lung injury	MCTRs	(100, 102)
ARDS	PCTR1	(103)
Skin and burn wound	RvD2	(70, 72)
Colitis/IBD	RvE1	(47)
	$RvD5_{n\text{-}3\ DPA}$, $PD_{n\text{-}3\ DPA}$	(108)
Arthritis	RvD1	(59)
	RvTs	(107)
	$RvD5_{n\text{-}3\ DPA}$	(114)
Periodontitis	RvD2	(156)
Regeneration	Planaria head regeneration: MaR1, RvE1, MACTRs, PCTRs, RCTRs	(24, 25)
	Bone: MaR1	(93)
	Muscle: RvD2	(71)
	Zebrafish fin regeneration: PD1	(157)
Alzheimer's disease	RvE1	(45)
Neuroinflammation	Neurocognitive disorders: MaR1	(91)
	Epileptogenesis: $PD1_{n\text{-}3\ DPA}$	(109)
Dermatitis	RvE1	(46)
Multiple sclerosis	RvD1, PD1	(22)
Cancer	RvE1, RvD1, RvD2	(48)
	17R-RvD1, 17R-RvD3	(57)
Atherosclerosis	RvE1	(43)
	$RvD5_{n\text{-}3\ DPA}$	(27)
Aortic aneurysm	RvD1	(136)
Depression	RvE3	(52)
Aging	RvD1	(58)
Parkinson's disease	RvD1	(60)
Sickle cell disease	AT-RvD1	(61)
Ischemia-reperfusion kidney injury	RvD1	(67)
Deep vein thrombosis	RvD4	(81)
Neuropathic and inflammatory pain	RvD5	(83)
	MaR1	(92)
Traumatic brain injury	NPD1	(85)
Stroke	NPD1, 17R-NPD1	(86, 87)

Diseases/conditions	SPMs that resolve inflammation and reduce disease severity	Reference
Skin inflammation	MaR1	(94, 95)
Cystic fibrosis	RvD1	(120)