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Resolvins and Cysteinyl-containing Pro-Resolving Mediators Activate Resolution of Infectious Inflammation and Tissue Regeneration

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Abstract

This review is a synopsis of the main points from the opening presentation by the authors in the Resolution of Inflammation session at the 8th European Workshop on Lipid Mediators held at the Karolinska Institute, Stockholm, Sweden, June 29th, 2022. Specialized pro-resolving mediators (SPM) promote tissue regeneration, control infections and resolution of inflammation. These include resolvins, protectins, maresins and the newly identified conjugates in tissue regeneration (CTRs). We reported mechanisms of CTRs in activating primordial regeneration pathways in planaria using RNA-sequencing. Also, the 4S,5S-epoxy-resolvin intermediate in the biosynthesis of resolvin D3 and resolvin D4 was prepared by total organic synthesis. Human neutrophils convert this to resolvin D3 and resolvin D4, while human M2 macrophages transformed this labile epoxide intermediate to resolvin D4 and a novel cysteinyl-resolvin that is a potent isomer of RCTR1. The novel cysteinyl-resolvin significantly accelerates tissue regeneration with planaria and inhibits human granuloma formation.

Keywords

human leukocytes; neutrophils; M2 macrophages; wound healing

Introduction

Excessive or uncontrolled inflammation is now widely recognized as a key process underlying the pathological feature for many diseases including cancer, arthritis, metabolic syndrome, chronic pain, periodontal, cardiovascular and neurological diseases, as well as

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bacterial and viral infections, such as Coronavirus Disease 2019 (COVID-19) [reviewed in 1, 2]. The acute inflammatory response is normally a protective mechanism that should ideally be self-limited. This physiologic response enables repair of injured tissues and the elimination of invading organisms and/or toxic materials, thus leading to complete resolution of the leukocyte infiltrates and clearance of cellular debris and microbes enabling homeostasis [1, 3]. Focusing on fundamental mechanisms in the resolution responses, the Serhan laboratory uncovered several novel families of pro-resolving lipid mediators (LMs) of inflammation from self-resolving inflammatory exudates that demonstrated potent bioactions in key cellular systems known to be involved in the resolution phase of the acute inflammatory response (Figure 1). These new compounds, born in Boston, MA beginning in 2000 [4] and first presented at the Florence meeting on eicosanoids in Italy that same year, are biosynthesized from the essential polyunsaturated fatty acid precursors, e.g. eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and n-3 docosapentaenoic acid (DPA) (Figure 2). Given their potent stereoselective actions with isolated human neutrophils and in vivo in mouse inflammation models promoting resolution, these potent endogenous bioactive molecules were named resolvins (Rv), protectins (PD), their aspirin-triggered (AT) epimers, and maresins (MaR); they together constitute a superfamily coined specialized pro-resolving mediators (SPMs) because of their highly specialized cellular functions in the resolution of inflammation and tissue injury, microbial clearance and reducing pain.

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 [reviewed in 1] 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 [1], since they were rapidly made commercially available for academic use by several companies. This review focuses on the EPA- and DHA-derived SPMs. For an overview of the n-3 DPA-derived SPMs, please see the recent review and references within [5].

The real scoop on the SPMs: as presented for the Workshop participants

Each family of SPMs was isolated from biologic fractions of resolving inflammatory exudates, and basic structures of the bioactive material were determined using chemical degradation methods, derivatives and physical methods; for example, see [4].

E-series resolvins: EPA-derived resolvins

- RvE1 –
  - First identified SPM from self-resolving murine exudates with modeled biosynthesized via human PMN-endothelial cell-cell interactions during co-incubations. We used several bioassays to study the resolution of inflammation [4]. Results from these studies demonstrated that RvE1 reduced PMN trans-endothelial migration, cleared acute inflammation in the mouse air pouch, and partially competed for ^{3}H-LTB$_4$ binding with recombinant human BLT1 cell surface receptor.

  - Complete stereochemistry of RvE1 was established next, and a second RvE1 receptor identified, i.e., human ChemR23 [6].
  - A synthetic RvE1 stable analog mimetic, i.e., 19-(p-fluorophenoxy)-RvE1, that resists rapid metabolic inactivation, retains biological activity reducing PMN infiltration and pro-inflammatory cytokine/chemokine production in vivo, was prepared, demonstrating potent pro-resolving activity in mice in vivo [7].
  - >275 publications confirming RvE1 production and functions are in PubMed.gov to date.

- RvE2 –
  - Identified in human PMN and reduces PMN infiltration in vivo [8].
  - Identified from self-resolving exudates and stops PMN chemotaxis and phagocytosis [9]. For a recent detailed review of the biosynthesis pathway and original studies, interested readers are urged to see [10].
  - Benzene congeners of RvE2, i.e., o-, m-, and p-BZ-RvE2, exhibiting much higher metabolic stability and more potent than RvE2, are active in femtogram ranges in reducing PMN infiltration in murine peritonitis [11].
- RvE3 –
  - Biosynthesized by eosinophils via the 12/15-lipoxygenase pathway, born in Japan in Professor Arita's lab, limiting PMN infiltration in zymosan-induced peritonitis [12].
  - Total organic synthesis of RvE3 and bioactions has been carried out [13].
- RvE4 –
  - Identified during studies of macrophage-PMN interactions in physiologic hypoxia conditions and stimulates efferocytosis [14].
  - Total organic synthesis of RvE4 confirmed the actions of proposed biogenically-prepared structure, complete stereochemistry assignment and function [15].
  - The second total organic synthesis, achieved with Professor Trond Hansen‟s team in Oslo, was also reported for RvE4, which physical properties (UV-Vis and LC-MS/MS) match those obtained from biological materials [16].
  - RvE4 is produced in humans; its levels are lower in cerebrospinal fluid from patients with Alzheimer's disease compared to those with subjective cognitive impairment [17].

D-series resolvins: DHA-derived resolvins RvD1-RvD6, identified from self-resolving murine exudates, biosynthesized via human endothelial-PMN interactions under

hypoxia conditions, and reduces microglial cell cytokine expression as well as in vivo dermal inflammation and peritonitis [18, 19]. As of February 2023, there are >1,590 publications using the search term “resolvin” on PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=resolvin&sort=date) confirming the potent pro-resolving actions of resolvins and their in vivo biosynthesis.

- RvD1 –
  - Total organic synthesis of RvD1 was used to establish its complete stereochemistry and confirm potent bioactions of RvD1 in vitro and in vivo [20].
  - A metabolically stable analog 17R-hydroxy-19-para-fluorophenoxy-resolvin D1 methyl ester was prepared, that reduces lung vascular permeability, PMN and inflammatory cytokines in immune complex-induced lung injury [21].
  - >560 publications confirm RvD1 biosynthesis and functions from many independent laboratories around the globe (see PubMed.gov).
- RvD2 –
  - Complete stereochemistry of RvD2 was established [22]; RvD2’s displays potent stereoselective actions in reducing PMN trafficking to inflammatory loci and controls microbial sepsis [22].
  - >130 publications from independent labs confirm our original RvD2 biosynthesis, structure, and functions.
- RvD3 –
  - Complete stereochemistry of RvD3 was established; synthetic RvD3 potently regulates murine peritonitis and dermal inflammation, as well as leukocyte-directed actions with human cells [23].
- RvD4 –
  - Total synthesis of RvD4 established its absolute stereochemical configuration; synthetic RvD4 reduces PMN infiltration in vivo and enhances uptake of apoptotic PMN by human dermal fibroblasts [24], the main processes in the resolution response phase of the acute inflammatory response in vivo.
  - RvD4 also reduces the severity of deep-vein thrombosis in vivo and improves thrombus resolution [25].
- RvD5 –
  - Controls murine E. coli and S. aureus infections in an anti-phlogistic manner, enhancing containment by the host of the invading microbes and lowers antibiotic requirements for bacterial clearance [26].
- RvD6 –

- RvD6 isomer (RR-RvD6) promotes corneal wound healing and nerve regeneration [27].

Protectins/Neuroprotectins: When of neural origin, neuroprotectin (NPD) is used, and Protectin (PD) is used to denote its peripheral actions, a tissue address.

- PD1 –
  - Identified in blood, leukocytes, brain, and glial cells, reduces murine PMN in vivo and human glial cell cytokine production [19].
  - Complete stereochemical assignment of the potent bioactive PD1 was established; synthetic PD1 is a potent regulator of PMN infiltration in vivo [28]. For a detailed review of the biosynthesis of the Protectins, interested readers should see [29].
  - Neuroprotectin D1 was identified in neural stem cells, and promotes neuronal and cardiac differentiation [30].
  - >250 publications confirm PD1/NPD1 biosynthesis and potent functions (PubMed.gov).
- ePD (16S,17S-epoxy-PD) –
  - This epoxide is the intermediate and precursor of PD1 biosynthesis; total organic synthesis of ePD confirms its conversion to PD1 by human macrophages [31]. For a recent review, see [32].
  - ePD is bioactive; inhibits LTB_4 production [33].

Maresins: macrophage mediator in resolving inflammation

- MaR1 –
  - First identified in the later resolution phase of self-resolving inflammatory exudates when macrophages enter, carries potent anti-inflammatory and pro-resolving activity [34].
  - MaR1 stereochemistry was established using several isomers prepared by total organic synthesis; synthetic MaR1 confirmed its potent defining bioactions; namely, MaR1 stimulating efferocytosis, tissue regeneration and reducing pain [35].
  - ~450 publications on PubMed for the maresins, of which ~270 publications confirm both MaR1 production and its potent functions.
- MaR2 –
  - Human macrophages produce MaR2, biosynthesized via 12-LOX and soluble epoxide hydrolase; MaR2 is the second potent bioactive member of the Maresins, reduces PMN infiltration in mouse peritonitis and enhances human macrophage phagocytosis [36].
  - Brown adipose tissues produce MaR2, which reduces inflammation in obesity in part by targeting macrophages in the liver [37].

- eMaR (13S,14S-epoxy-maresin) –
  - This epoxide intermediate in MaR1 biosynthesis is bioactive, inhibiting LTB_4 production by LTA_4 hydrolase and promoting M2 macrophage phenotype [38]. For a detailed review of the mechanism of biosynthesis and original references, interested readers may see [29].

Human Resolution Metabolome

Production of SPMs in human tissues has been documented using mass spectrometry-based profiling approaches in more than 45 human trials using the current NIH definition of clinical trial (Table 1A). For example, human vagus nerves ex vivo produce SPMs, e.g., RvE1, NPD1/PD1, MaR1, upon electrical stimulation suggesting that these vagus-SPM circuits contribute to a new pro-resolving vagal reflex [39]. In the recent WARRIOR Trial, women with coronary microvascular dysfunction (CMD) had significantly lower plasma concentrations of RvD1 and MaR1 than the reference subject group [40]. Also, several randomized clinical trials demonstrate that omega-3 or marine oil supplementation increases SPMs in vivo in humans (Table 1B).

SPM-receptor pro-resolving axes

Each EPA- and DHA-derived SPM, including RvE1, RvD1, RvD2, PD1 and MaR1, exhibits potent stereoselective actions (pico- to low nanomolar concentrations) via activation of their specific G protein-coupled receptors (GPCR) on phagocytes and additional select cell types (Figure 3). The bioactive concentration ranges of SPMs are in the picomolar to low nanomolar ranges, consistent with the affinities of SPMs for their respective GPCRs (i.e., Kd values) (Figure 3). These GPCRs contribute to SPM functions as demonstrated in animal systems and select cell types in vivo and in vitro using transgenic and/or knockout mice, gene silencing, blocking antibodies and/or receptor antagonists (Table 2).

Receptor mimetics. Since SPMs are subject to rapid local metabolism in or near the site of inflammation via enzymatic inactivation, metabolically stable analogs that resist enzymatic inactivation were designed and synthesized [7]. Also, using a high-throughput screening of small-molecule libraries (>45,000 compounds), several chemotypes were identified to activate the RvD1 receptor (DRV1/GPR32) and stimulate macrophage E. coli phagocytosis in DRV1-dependent manner [41]. Further, different synthetic approaches have been employed for structural modifications of SPMs [reviewed in 42]. Together, these molecules act as receptor mimetics, offering potentially more cost-effective synthesis to facilitate clinical development of therapeutics that stimulate resolution pathways.

Where is resolution of inflammation important? What is the evidence?

Why do we study endogenous resolution mechanism of acute inflammation and pro-resolving mediators? The currently available pharmacopeia for treating inflammatory diseases consists mainly of enzyme inhibitors and receptor antagonists, which could lead to many unwanted side effects [1]. For example, non-steroidal anti-inflammatory drugs could cause prolonged neuropathic and inflammatory pain [43]. COX-2 inhibitors are known to

increase incidence of thrombosis and myocardial infarction [44, 45], and anti-TNFα therapy increases risk of infections [46]. Therefore, there is urgent need for new approaches in controlling excessive inflammation, e.g., SPMs as resolution agonists, that could spare these severe side effects. In this regard, the author (CNS) pointed out with the discovery of the first resolvin that the resolution phase of inflammation offers a new terrain to control the endogenous cellular mechanisms of inflammation in many diseases [47–49]. To pinpoint the actions in inflammation-resolution, we introduced quantitative indices (i.e., resolution indices, Ri) that demonstrate accelerated or delayed resolution [47–49].

SPMs are endogenous mediators that exhibit potent pro-resolving functions, limiting PMN and pro-inflammatory cytokines, while stimulating macrophage phagocytosis and efferocytosis [reviewed in 1] as well as activating autophagy [50]. In experimental in vivo systems, SPMs reduce collateral tissue damage, promoting tissue repair and regeneration as well as controlling pain [1]. These include neuroinflammation, pain, arthritis, periodontitis, cardiovascular diseases, lung inflammation and metabolic syndromes, to name just a few. These are the areas where resolution of inflammation is essential, and the goals of resolution pharmacology [51, 52] might be achieved in part via personalized profiling of resolution metabolomes and following specific SPM treatment to provide precision medicine to promote the natural endogenous active resolution pathway [47, 49].

- Neuroinflammation
  - In Alzheimer disease (AD), resolution of inflammation is impaired in the brain. NPD1 repressed Abeta42-triggered activation of proinflammatory genes while upregulating the antiapoptotic genes [53].
  - Intranasal delivery of a panel of SPMs rescues memory and gamma oscillation deficits as well as reduces microglial activation in AD mice [54].
- Pain
  - In inflammatory pain models: RvE1 reduces inflammatory pain behaviors induced by formalin, carrageenan and complete Freund’s adjuvant [55].
  - SPMs display potent analgesic actions, promoting resolution of pain in animal models of pathological pain [56]. RvD5 is the first SPM that shows sex dimorphism in pain regulation, inducing male-specific analgesia [57].
- Periodontitis and Arthritis
  - Periodontitis and arthritis are well-appreciated example of leukocyte-mediated inflammation and bone destruction. Failure of active resolution of inflammation pathways is implicated in disease pathogenesis.
  - Overexpression of 15-LOX, a key biosynthesis enzyme for many of the SPMs and LXs, in a large animal model is associated with

dampened PMN-mediated tissue degradation and reduced bone loss [58], suggesting that SPMs/LXs can be targets for novel approaches to diseases, e.g., periodontitis and arthritis.

- Topical application of RvE1 in rabbit periodontitis protects against inflammation-induced tissue and bone loss [59].
- D-series resolvins such as 17R-RvD1 and RvD3 reduce joint leukocytes, clinical scores and edema, as well as shorten the remission interval [60, 61].
- In a recent randomized trial with 127 individuals, daily use of an oral rinse containing a SPM stable analog and LXA_4 mimetic methyl ester-benzolipoxin A_4 ($BLXA_4$) reduces local inflammation and increases abundance of pro-resolution molecules systemically [62].

- Cardiovascular diseases
  - Atherosclerosis results from a failure in the resolution of local inflammation. Overexpression of 12/15-LOX protects mice against atherosclerosis via its role in the local biosynthesis of SPMs [63].
  - Administration of RvD1 to $Ldlr^{-/-}$ mice during plaque progression promotes plaque stability and improves lesional efferocytosis, and thickens fibrous caps [64].
- Lung inflammation
  - In a murine model of asthma, a stable analog of LXA_4 blocks both airway hyper-responsiveness and pulmonary inflammation [65].
  - In E. coli lung infection, 17R-RvD1 restores TLR9-mediated impaired neutrophil phagocytosis and accelerate resolution of lung inflammation [66].
  - In lung infections, Cys-SPMs MCTR1–3 decrease lung inflammation and bacterial load in Influenza A virus infections followed by secondary bacterial pneumonia [67].
- Metabolic syndromes
  - Obesity and obesity-related disorders are linked to a chronic state of low-grade inflammation in adipose tissue [68].
  - With inflamed obese adipose tissue, RvD1 and RvD2 each rescues impaired expression of adiponectin and decreases proinflammatory adipokine production, as well as reduces monocyte adhesion to adipocytes and their trans-adipose migration [69].
  - In obese-diabetic mice, RvD1 decreases adipose tissue macrophages and improves insulin sensitivity in part via increasing adipose tissue AMP-activated protein kinase (AMPK) phosphorylation [70].

- RvD1 directs pro-resolving metabolic programs in macrophages, promoting fatty acid oxidation and oxidative phosphorylation, in part via activation of AMPK phosphorylation [71].

- Aging
  - Aging delays resolution of acute inflammation in mice, and nano-pro-resolving medicine activates age-dependent resolution pathways [72].
  - RvD1 promotes efferocytosis and prevents MerTK cleavage in aging [73].

- Depression
  - There is an unmet need for novel rapid-acting antidepressants with fewer side effects than currently available monoamine-based antidepressants.
  - Resolvins (RvD1, RvD2, RvE1, RvE2 and RvE3) exert antidepressant effects in a rodent model of depression via mTORC1 activation [74].

Stereochemical assignment and biosynthesis of cys-SPMs

While interrogating self-resolving infectious exudates, the Serhan Lab uncovered three new series of conserved bioactive chemical signals that are peptide-lipid molecules, collectively termed cysteinyl-SPMs (cys-SPMs). These include three series, i.e., maresin conjugates in tissue regeneration (MCTRs), protectin-CTR (PCTRs) and resolvin-CTR (RCTRs) based on their DHA backbone and family structures [75] (Figure 4A). Each series contains three bioactive members, i.e., MCTR1–3, PCTR1–3 and RCTR1–3. Cys-SPMs exhibit pro-regenerative actions with freshwater Planaria, and also demonstrated classic pro-resolving functions such as limiting polymorphonuclear neutrophil (PMN) infiltration and enhancing MΦ phagocytosis and efferocytosis [75, 76].

The complete stereochemical assignments of these nine potent cys-SPMs, i.e., MCTR1–2, PCTR1–3 and RCTR1–3 were established, and total organic synthesis achieved [75, 76], permitting demonstrations of their potent actions. See Table 3 for the complete stereochemical names and identifiers on Lipid Maps and PubChem. Biosynthesis metabolomes of MCTRs and PCTRs were established, and enzymes involved in their biosynthesis determined. During self-limited E. coli peritonitis in mice, endogenous MCTRs, PCTRs and RCTRs are produced time-dependently in infectious peritoneal exudates and distal spleens [33]. With human recombinant enzymes, PCTR1 and MCTR1 are each produced by leukotriene (LT) C_4 synthase (LTC_4S) and glutathione S-transferases (GSTs) [microsomal GST (mGST)2, mGST3, and GST-μ (GSTM)4] from their epoxide precursors [16S,17S-epoxy-PD (ePD) and 13S,14S-epoxy-MaR (eMaR)] (Figure 4B). Human M2-like macrophages express LTC_4S, mGST2, mGST3, and GSTM4 and produce cys-SPMs [33]. These results demonstrate CTR biosynthesis in mouse tissues and human macrophages, as well as identified key enzymes in these pathways.

cys-SPM production and functions

cys-SPMs are evolutionarily conserved molecules from planaria, mouse to human. They were originally isolated in planaria and mouse infectious exudates [75]. cys-SPMs were also identified in numerous human tissues and cells, such as serum, plasma, lymph nodes, brain, bone marrow [75], macrophages [33] and platelets [77]. Recently, periodontal stem cells were found to biosynthesize MCTR3 [78]. See Table 4 for further details.

In additional to the pro-regenerative actions of cys-SPMs in primordial organism freshwater planaria, cys-SPMs exhibit potent actions in experimental mammalian systems controlling inflammation and infection and are organ protective (Table 5). The first identified cys-SPM series MCTRs protect cardiovascular systems in mice and in primordial sea squirt, as well as counter LTD_4-initiated signals and vascular response [79]. Each MCTR (10–100 nM) significantly reduced LTD_4-initiated signaling via the recombinant human cysteinyl leukotriene receptor-1 (cysLT1) [79]. In murine allergic airway inflammation, MCTRs block LTD_4-induced airway contraction [80, 81]. Most recently, MCTR3‴s protective actions in airway hyperresponsiveness were demonstrated to be cysLT1-dependent using cysLT1 deficient mice [82].

Following our initial identification and structural elucidation of cys-SPMs as well as demonstration of their pro-regenerative and pro-resolving actions, their potent actions have been extended to many experimental disease systems. For example, cys-SPMs control both bacterial and viral infections. In S. aureus infectious skin wound, PCTR1 stimulates wound closure and reduces bacterial titers [83]. In a Respiratory Syncytial Virus (RSV, which is currently widely in the news given the very high number of infections worldwide) pneumonia model, PCTR1 decreases viral load [84]. In bacterial pneumonia and viral Infection, MCTRs decrease lung inflammation and bacterial titers [67]. MCTRs are also organ protective in acute kidney and cardiac injury, hepatic ischemia-reperfusion and arthritis (see Table 5 for details and references).

With human cells, cys-SPMs demonstrate cell type-specific pro-resolving functions. Each of the nine cys-SPMs stimulates human macrophage phagocytosis and efferocytosis. In addition, RCTRs reduce PMN chemotaxis and adhesion, and PCTR1 promotes keratinocyte migration [83] and Increases IFN-lambda in bronchial epithelial cells [84]. 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 (Table 5).

cys-SPMs activate resolution-regeneration pathways and effectors

In order to assess the regenerative capacity of cys-SPMs, we used freshwater planaria because planaria are known to undergo robust regeneration via primordial pathways [85]. Each of the cys-SPMs promotes planaria head regeneration [76], permitting us to evaluate molecules and pathways activated by each cys-SPM. RNA-sequencing (RNA-seq) was carried out with surgically injured planaria and cys-SPMs; see [86] and Figure 5. The third member in each cys-SPM biosynthetic pathway was selected for these studies, namely MCTR3 (13R-cysteinyl-14S-hydroxy-4Z,7Z,9E,11E,16Z,19Z-docosahexaenoic

acid), PCTR3 (16R-cysteinyl-17S-hydroxy-4Z,7Z,10Z,12E,14E,19Z-docosahexaenoic acid) and RCTR3 (8R-cysteinyl-7S,17Sdihydroxy-4Z,9E,11E,13Z,15E,19Z-docosahexaenoic acid), because each potently enhances regeneration. Following planaria (D. japonica) head resection, MCTR3, PCTR3, RCTR3 separately at 10 nM each or control was administered in water. Planaria were collected at 48h and mRNA was isolated for RNA-seq. Transcript abundance was obtained by generating gene counts using paired-end sequences [87], and reads were assembled using the Trinity program with Dj transcript sequences [88]. All coding sequences were translated into deduced peptide sequences, and genome-wide functional annotation was obtained via orthology assignment by eggNOG-mapper [89].

To identify gene and pathways significantly regulated by each of the bioactive cys-SPM, a Wald test was carried out using the R package sleuth to compare all groups to obtain the P-value, false discovery rate (FDR), i.e. adjusted P-value using Benjamini-Hochberg method), and the 'beta' value (analogous to fold change). The „beta" value (analogous to fold change) was obtained by comparing control (injured planaria with vehicle) vs. MCTR3, PCTR3 or RCTR3 using the transcript abundance (log_2TPM) for each transcript. Pathway enrichment was assessed with the mean-rank gene set test (geneSetTest function in the R package limma) against the Canonical Pathways (CP) and Gene Ontology (GO) pathway databases. Interested readers are referred to [86] for further details. Among the total of 33,511 transcripts obtained, we focused on those shared transcripts increased by the 3 cys-SPMs; they up-regulated 175 known transcripts with predicted functions (FC>1.25). Further pathway and transcript analyses converged on TRAF3 [86], a "gatekeeper" controlling TLR and TNFR signaling pathways [90]. Therefore, we next focused on TRAF3 network analysis using Cytoscape and BioGrid interaction. Within this network, the up-regulated transcripts TRAF5, ABCC, BIRC2 and USO1 and down-regulated transcripts USP7 and OTUD5 by cys-SPMs could potentially interact with TRAF3 [86].

For human translation, we examined the functions of cys-SPMs and TRAF3 with human macrophages since macrophages are essential for tissue resolution, repair and regeneration [91]. MCTR3, PCTR3 and RCTR3 each selectively enhances transcript and protein levels of TRAF3 via a G protein-dependent cAMP-PKA pathway in human MΦ during microbial challenge and stimulated phagocytosis of E. coli. A downstream effector of TRAF3, i.e., IL-10, is also up-regulated during phagocytosis. In addition, overexpression of TRAF3 in human macrophages increases phagocytosis via an IL-10-STAT3 pathway. In vivo in mice, TRAF3 silencing hampers phagocyte functions and resolution of E. coli infection. These results with mice and human MΦ demonstrate a cys-SPM-TRAF3-IL10 pro-resolving axis (Figure 6).

TRAF3 contributes to cys-SPM's pro-resolving programs, governing planaria regeneration, immune response with human phagocytes and in mice. Besides its functions in controlling TLR and TNFR signaling pathways in innate immunity, TRAF3 is also a negative regulator of platelet activation and thrombosis [92] and promotes antiviral signaling and type I interferon production upon RNA virus infections [93, 94]. Along these lines, resolvins reduce thrombosis [25], control influenza virus infections [reviewed in 5], limit SARS-CoV-2 Spike protein-induced cytokine storm [95], and attenuate NETs [96]. These protective actions of SPMs and TRAF3 are of interest and may be of clinical

interest considering the SARS-CoV-2 pandemic, where cytokine storms and increased coagulopathies are associated with the disease pathologies [97, 98]. We presented new results, not reviewed herein in detail, on human neutrophil extracellular traps (NETs) that play a critical role in bacterial and viral infections, as in SARS-CoV-2 infections. We also showed in this presentation on the newly identified RvTs (13-series resolvins) regulating NET formation. Using microfluidic devices capturing NETs with human whole blood, resolvin D2 and the RvTs each potently (RvT1-RvT4; 2.5 nM) reduces NETs; interested readers are referred to [96] for further details. These new results provide evidence that resolvins reduce NETosis and enhance macrophage NET clearance to promote resolution.

By using planaria as a model organism/system for temporal tissue regeneration with RNA-seq, we identified the cys-SPM-activated pathways during regeneration including TRAF3. With human macrophages, cys-SPMs each increases TRAF3, which regulates phagocyte functions and promotes resolution of infection (Figure 6). We also presented at the workshop the total organic synthesis of the proposed 4S,5S-epoxy-resolvin intermediate, deduced from acid methanol trapping [18, 20], in the biosynthesis of RvD3 and RvD4. Human neutrophils convert this synthetic intermediate to RvD3 and RvD4, whereas human M2 macrophages transform this labile epoxide intermediate to RvD4 and a novel cysteinyl-resolvin that proved to be a positional isomer of RCTR1 [99]. This short-lived intermediate in the biosynthesis pathway, 4S,5S-epoxy-resolvin, was prepared by total organic synthesis [100] and subject to non-enzymatic aqueous hydrolysis to produce four distinct non-enzymatic products; please see [99] and supplement within for mechanistic details. These studies are reported with Professor Jesper Haeggström and Prof. Bengt Samuelsson of the Karolinska (Stockholm, Sweden). This novel cysteinyl-resolvin, termed 4,5-RCTR1, was recently synthesized via total organic synthesis. Its complete stereochemistry and bioactions are reported in[1].

M2 macrophages play key roles in the resolution of inflammation and wound healing. Human M2 macrophages also converted leukotriene A_4 to lipoxins; see [99] and supplement within. The novel cysteinyl-resolvin, 4,5-RCTR1, significantly accelerated tissue regeneration of surgically injured planaria. In a model of human granuloma formation, this novel cysteinyl-resolvin isomer significantly inhibited granuloma development by human peripheral blood leukocytes. These results provide evidence for human cell type-specific role of 4S,5S-epoxy-resolvin in the biosynthesis of RvD3 by human neutrophils, RvD4 by both human M2 macrophages and neutrophils, and a novel cysteinyl-resolvin positional isomer produced by M2 macrophages that processes potent activities in granuloma formation, resolution, and tissue regeneration. In comparison, biosynthesis of RvD1 and RvD2 is via a 7S,8S-epoxy-resolvin intermediate [20]. Targeting cys-SPM network could provide approaches for controlling infections, protecting from organ injury, wound healing, and inflammatory diseases where tissue regeneration and control of unresolved inflammation are critically needed.

[1]Robert Nshimiyimana, Stephania Libreros, Melissa Simard, Nan Chiang, Ana R. Rodriguez, Bernd W. Spur and Charles N. Serhan. Phagocyte functions and total organic synthesis of 4*S*,5*R*-RCTR1 in the resolution of inflammation (submitted for publication)

Perspective

SPM are now proven to have a wide range of actions that open a new area for resolution physiology and pharmacology, where the mediators and their precursors are vital in supplying chemical signals for catabasis to homeostasis. These findings from our and other laboratories worldwide raise additional questions to be addressed. For example, regarding molecular and cellular mechanisms, are there overlapped and/or distinct signaling pathways in the SPM-receptor networks? Also, are there specific target cells in addition to phagocytes that express SPM receptors with cell-type dependency? Regarding SPM clinical development, the endogenous human formation of SPMs, their efficacy and optimal levels needed to promote timely resolution are of interest. Can we further develop personalized nutrition and supplementation to boost SPM production in men, women, children and the elderly? In this context, EPA supplementation dose-dependently (1, 2 and 4g/day) increases 18-HEPE in human circulation, which inversely associates with both systemic inflammation (plasma HPR levels) and symptoms of depression [103]. The field of resolution needs more clinical studies like this. Since SPM spatial-temporal resolution-metabolomes in humans are under intensive investigation (Table 1), and SPM-receptor networks with their structure-function relationships have been studied in many experimental systems (Table 2), then we can expect that more evidence will be published in the near future to support the pro-resolving functions of SPMs in human wellness and disease.

Conclusion/Summary:

In this invited review, we give a synopsis of the pro-resolving mediators, their discovery and their new roles in tissue regeneration, as presented at the workshop in Stockholm in the summer of 2022. The rigorous structural elucidation of the novel resolution phase of inflammation mediators, their defining cellular actions and biosynthesis from the Serhan laboratory are confirmed by many independent laboratories worldwide as reported in PubMed.gov (>1594 publications for resolvins, >2380 for lipoxins and >457 for maresins). These publications use available synthetic SPMs that are well-defined with complete stereochemistry, and extend the biologic impact and systems originally reported from the Serhan lab and cited herein. The evidence should be clear to all serious investigators that the SPMs are potent pro-resolving molecules, confirmed by many independent laboratories. Recent publications on the identification and SPMs in human and animal tissues as in [101,106,112] (see Table 1) should be taken seriously by the lipid mediator community, as well as the many other independent studies that report confirmation, extend and improve the SPM LC-MS-MS-based profiling and functions we introduced in [102]. At this workshop, CNS proclaimed our research mission in the Serhan Lab is to “uncover new approaches to control excessive inflammation that will not harm individuals and will lead to endogenous resolution of inflammation and tissue repair”. This is urgently needed because of the many diseases now widely recognized to have uncontrolled excessive inflammation, a major component in disease pathologies. As with all discoveries and new fields of research that emerge from them, there also rise “critics”. Here, we call on the famous quote of Professor Max Planck[2] that addresses this very situation with his own research in quantum physics. There can be no doubt, today that the study of SPMs and their potent pro-resolving properties can offer new directions to help in many maladies and infections (both bacterial

and viral). Can we really afford in these pandemic times not to dig deeper and do our very best for humanity as biomedical scientists?

Exciting research now opens as we await the next EU workshop. At the recent Eicosanoid Research Conference, November 2022 in New Orleans USA, of the 225 presentations at this international meeting, a substantial number of presentations showed exciting new results on the SPMs for resolvins, protectins and maresins from investigators around the world. Thus, the chapter on SPMs in human biology and medicine is open and continues to evolve, onward and upward. Please keep in mind that in the case of the prostaglandins, SPM forefathers, the first prostaglandins were identified in the 1930s with their complete structures and biosynthesis established in the 1960's and 1970's. Their exciting biology is still unfolding and remains widely studied today. As with prostaglandin research, some issues remain for the SPMs.

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[2]"A scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die and a new generation grows up that is familiar with it." Max Planck.

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Highlights

- Resolution of inflammation is governed by specialized pro-resolving mediators (SPM).
- SPM structural elucidation and complete stereochemistry are established.
- Mass spectrometry-based profiling document SPMs in human and animal systems.
- SPMs are pro-resolving, organ protective, control pain and infections.
- SPMs evoke pro-resolving functions via specific GPCRs in nanomolar ranges.

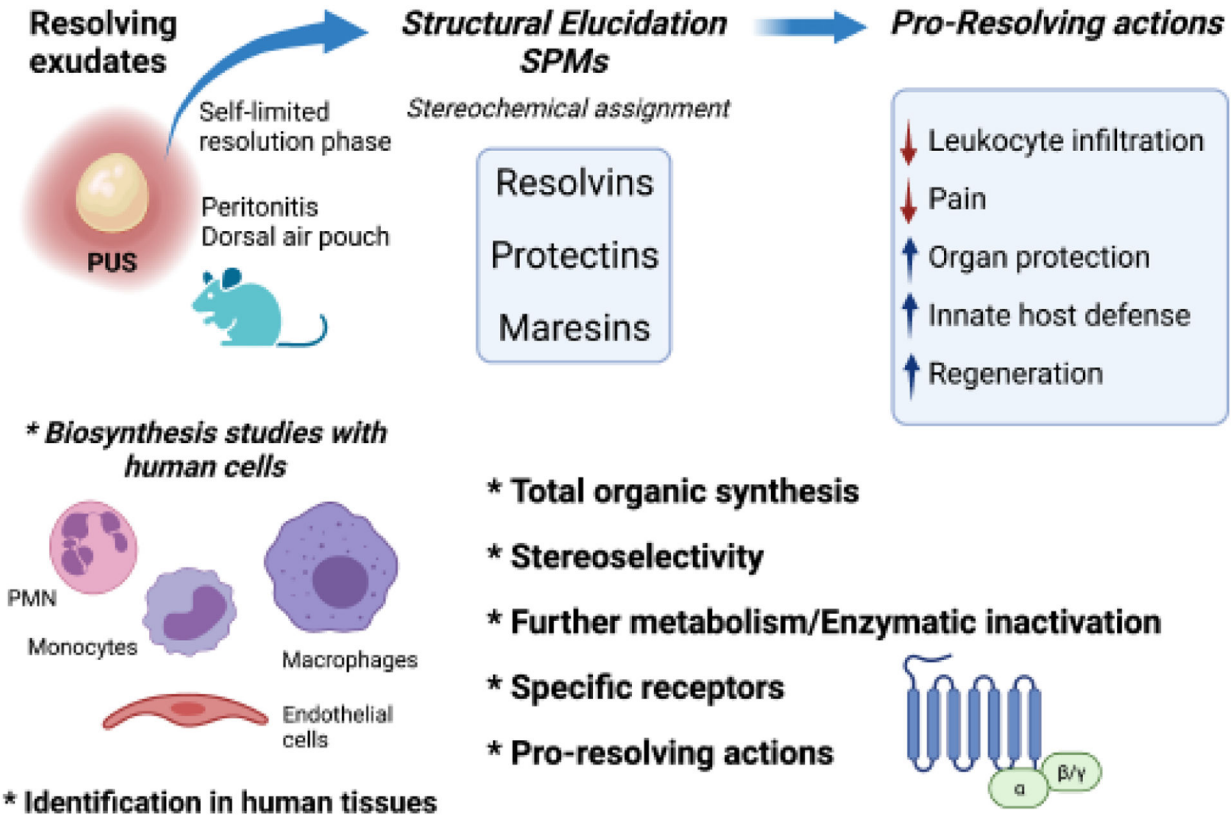
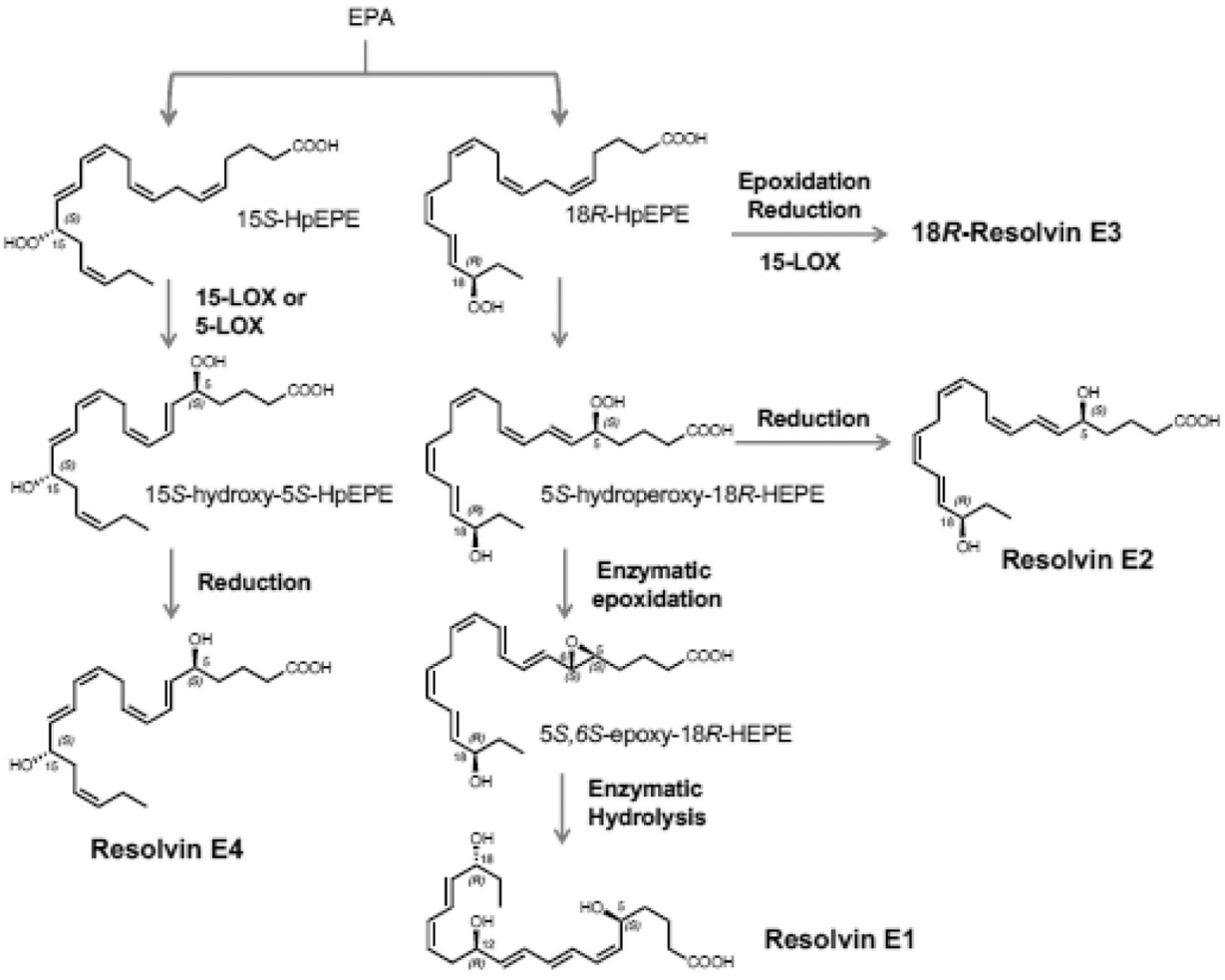
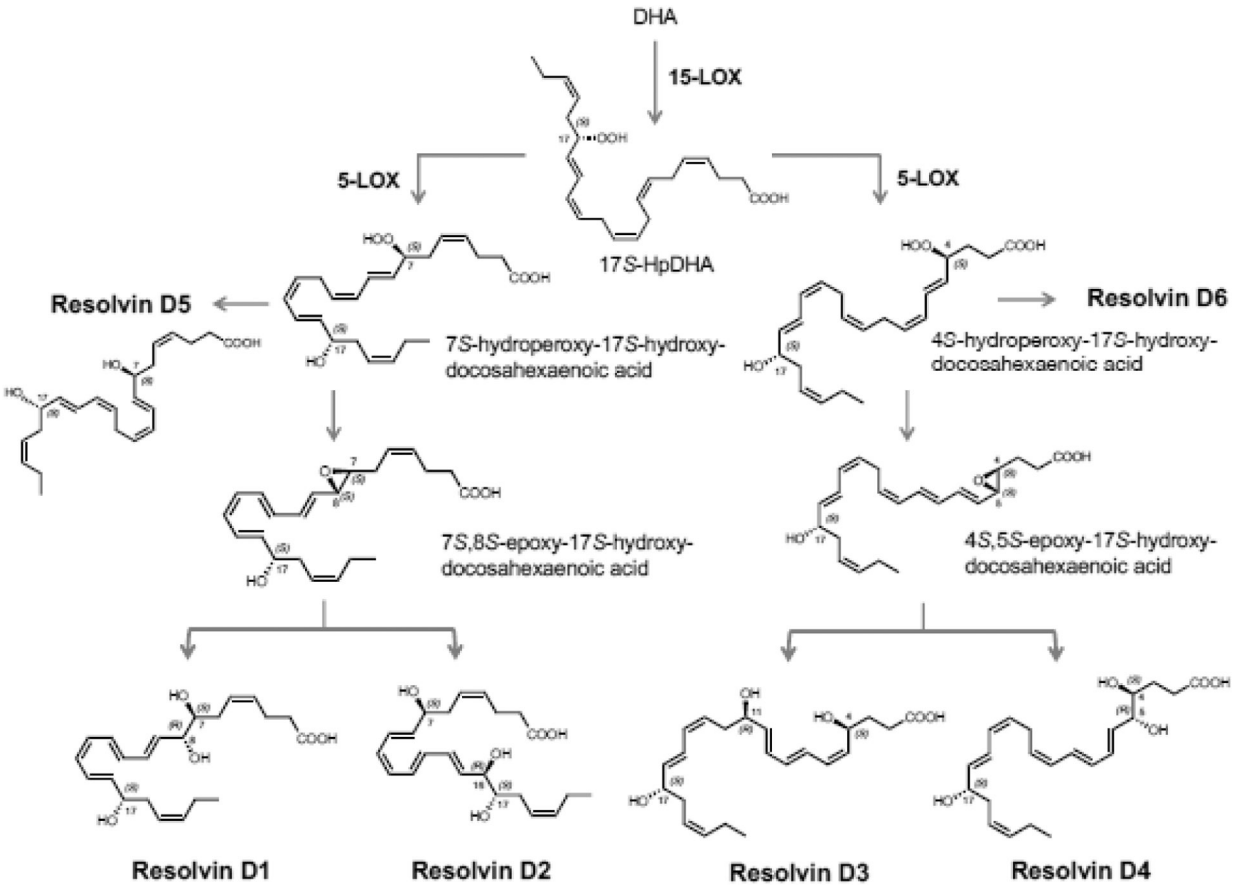


Figure 1. Overall strategy in the SPM elucidation of structures and functions

The first SPM, resolvin E1, was identified from resolving exudates in the Serhan lab in Boston, MA nearly 20 years ago [4], and SPM structure elucidation systematically carried out using a systems approach. With our Program Project team, we achieved complete stereochemical assignment of each bioactive SPM. In parallel, biosynthesis of SPMs was established with human cells, and their production in human tissues was documented. Following structural elucidation, total organic synthesis was achieved, stereoselectivity and further metabolism profile for each SPM were determined. Specific SPM cell surface receptors were identified, and SPM-receptor mediated potent pro-resolving actions were confirmed, such as reducing leukocyte infiltration and pain, promoting organ protection.





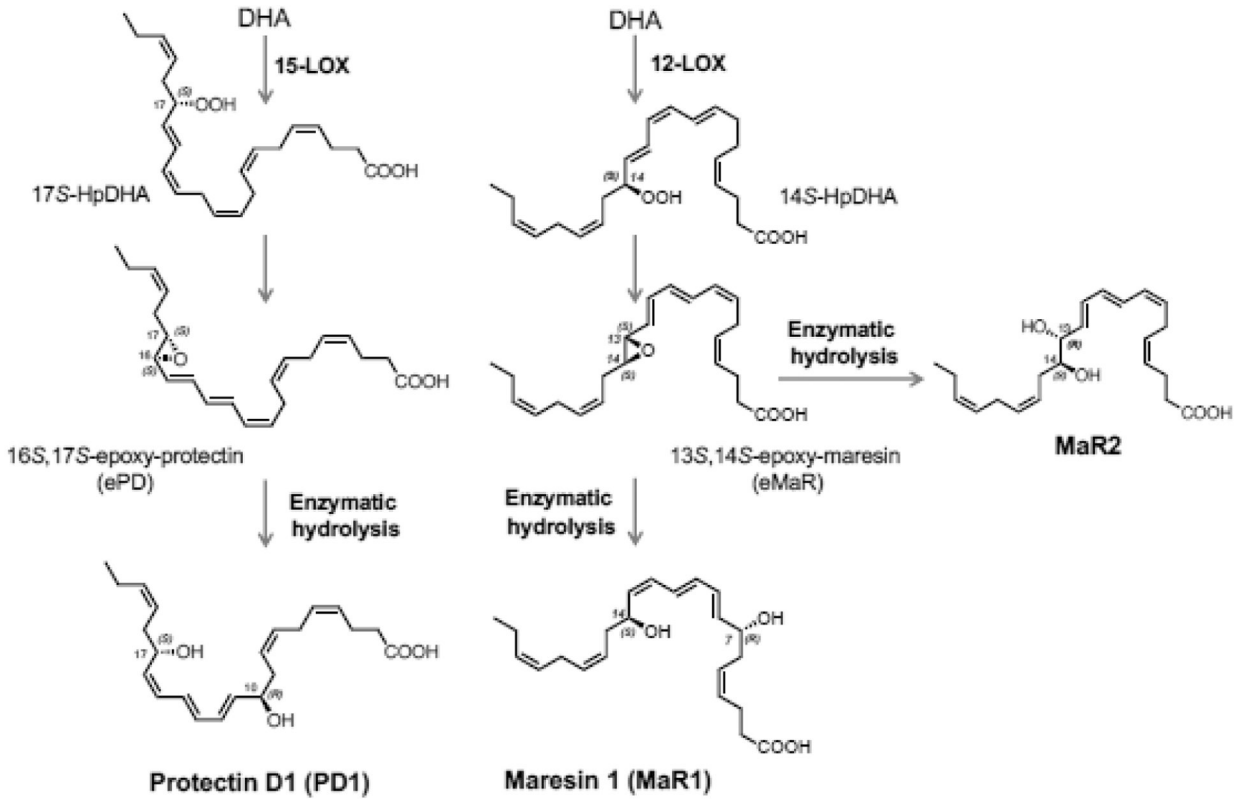


Figure 2. Biosynthesis of resolvins, protectins and maresins

(A) Biosynthesis of E-series resolvins is initiated via lipoxygenation of EPA at carbon-18 position to form 18-HpEPE, which is converted to bioactive E-series members resolvin E1, resolvin E2 and resolvin E3. A new bioactive member, termed Resolvin E4, was recently elucidated and stereochemistry established.

(B) Biosynthesis of D-series resolvins is initiated via 17-lipoxygenation of DHA to form 17S-HpDHA, which is converted to resolvin-epoxide intermediates by the leukocyte 5-lipoxygenase to resolvins D1-D6.

(C) 17S-HpDHA is also converted to 16S,17S-epoxide-protectin intermediate that is further transformed to protectin D1/neuroprotectin D1 and related protectins. Maresins are produced by macrophages via initial lipoxygenation at carbon-14 position by lipoxygenation to produce a 13S,14S-epoxide-maresin intermediate that is enzymatically converted to maresin family members. For original reports, total organic synthesis and stereochemical assignments, see text and cited recent reviews with original citations for details.

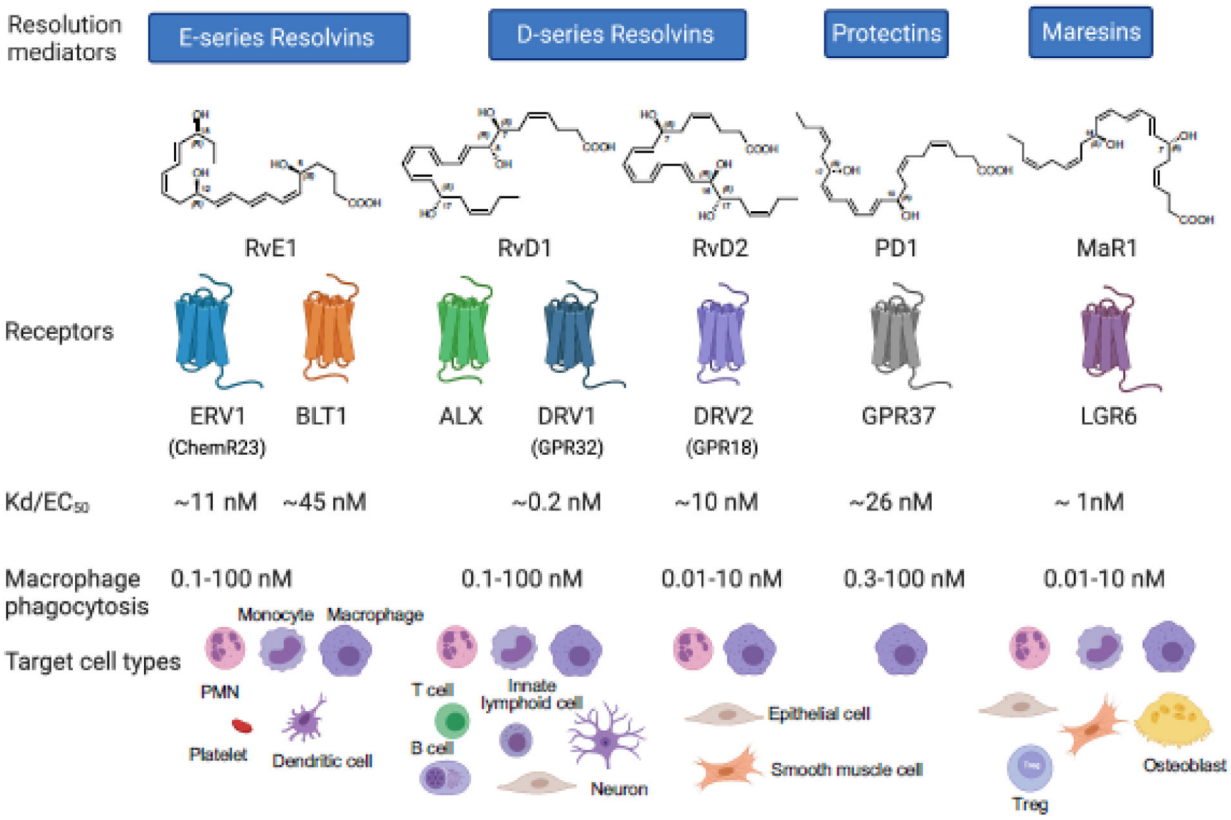
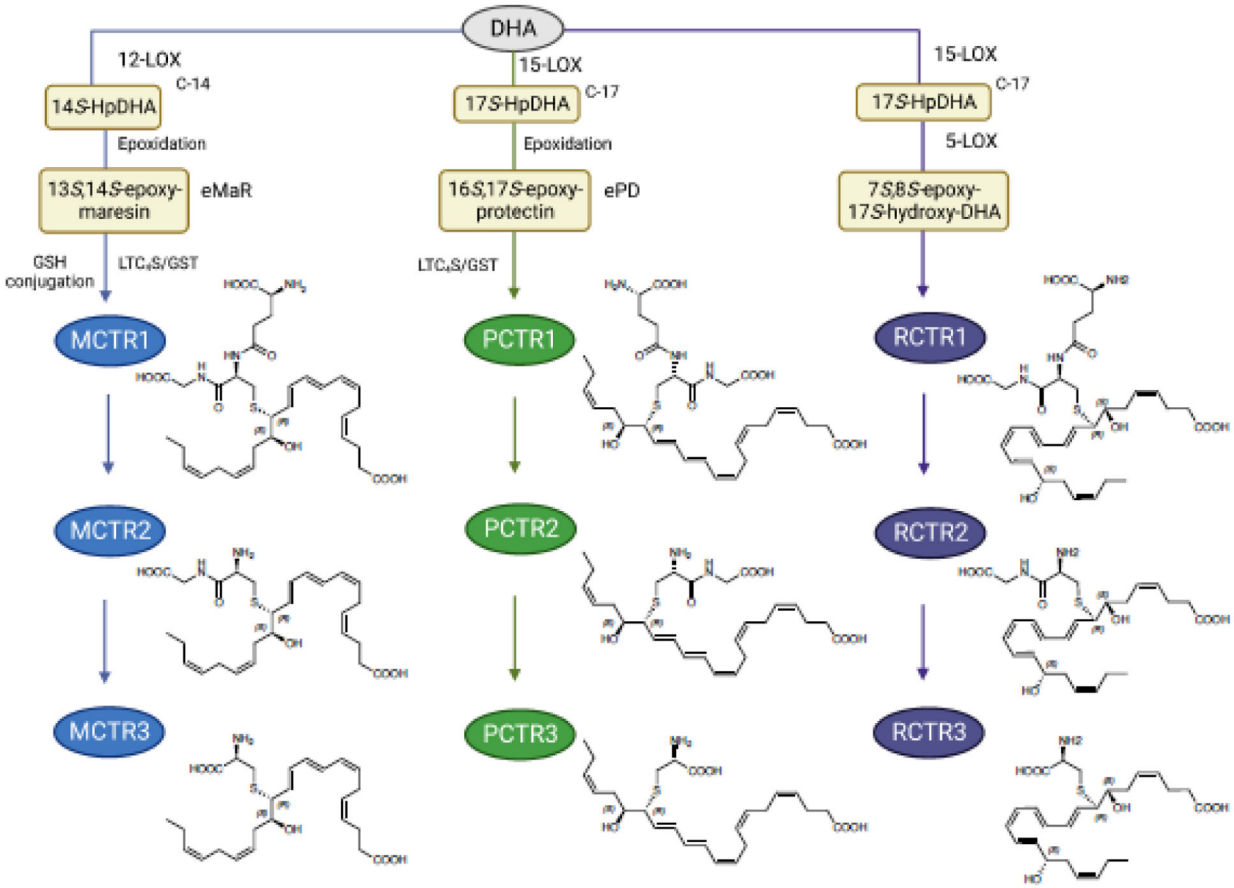


Figure 3. SPM receptors

Each SPM demonstrates stereoselective activation of its cognate GPCR on select cell types, leading to intracellular signals, pathways, and pro-resolving functions. The affinities of SPMs for their respective recombinant GPCRs (i.e., Kd or EC_{50} values) are consistent with their bioactive concentration ranges, e.g., macrophage phagocytosis (picomolar to low nanomolar) in vitro and dose ranges (picograms to low nanograms) in vivo. The in vivo functions of these SPM receptors were demonstrated using transgenic and/or knock-out mice, as well as specific blockage of the receptor, e.g., siRNA, antibodies, or receptor antagonists (see Table 2).



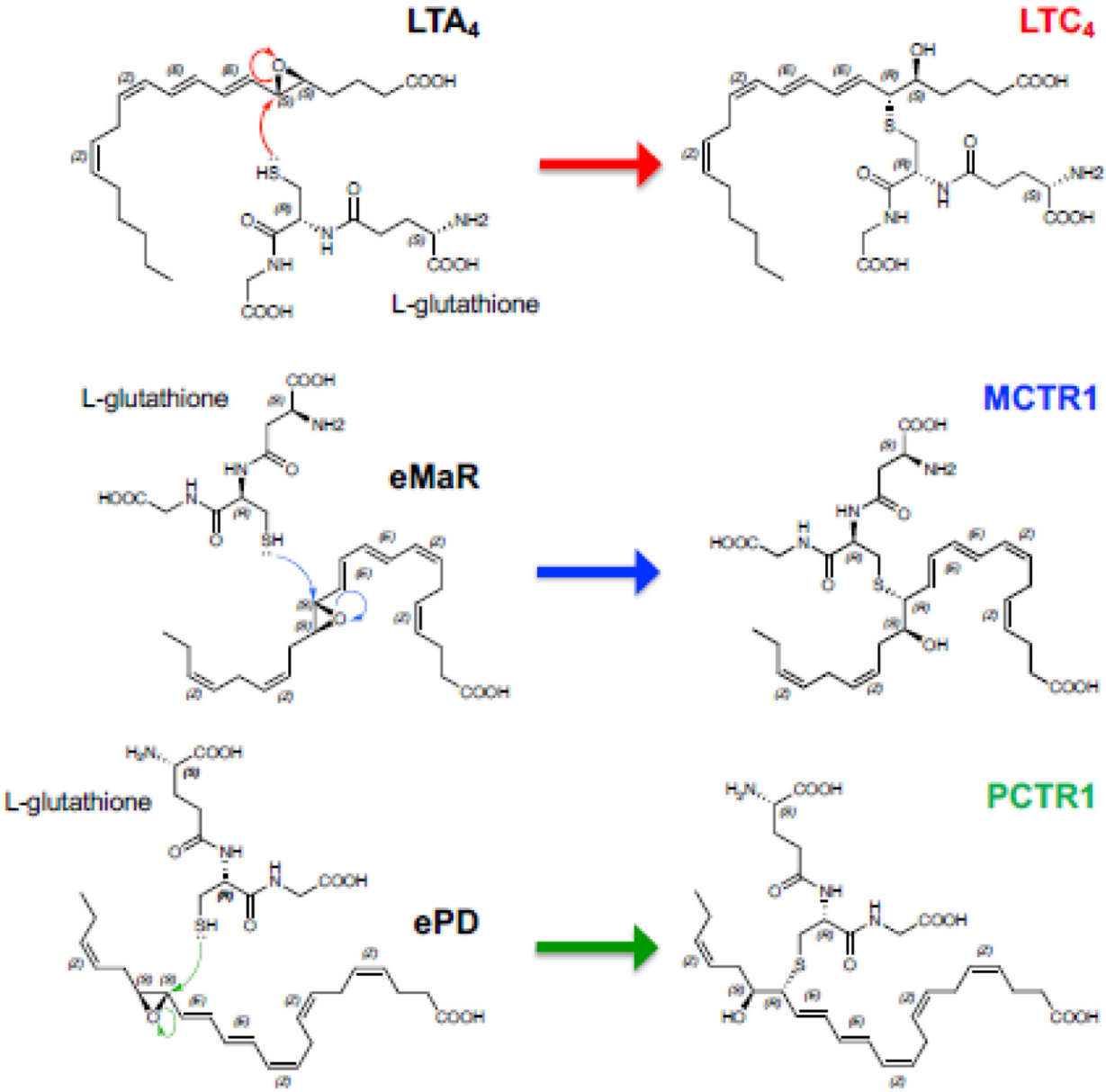


Figure 4. Biosynthesis of cysteinyl-SPMs.

(A) Biosynthesis of MCTRs, PCTRs and RCTRs (see text for details).

(B) Formation of cysteinyl-SPMs by conjugation of the epoxides with L-glutathione via stereoselective enzymatic mechanism.

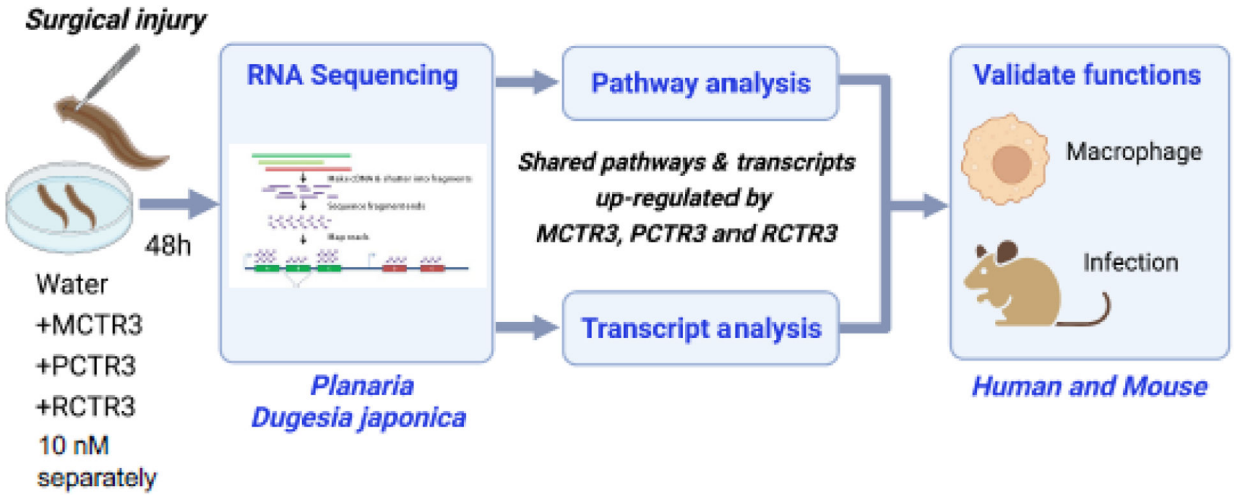


Figure 5. Strategy to identify resolution-regeneration effectors

Following planaria (D. japonica) head resection, MCTR3, PCTR3, RCTR3 separately (10 nM each) or vehicle control was administered in water. Planaria were collected at 48h and mRNA isolated for RNA-seq. Transcript and pathway analysis were carried out, and we focused on the shared transcripts and pathways increased by the 3 cys-SPMs, and validated their functions in mammalian systems using human macrophages and mouse in vivo infection.

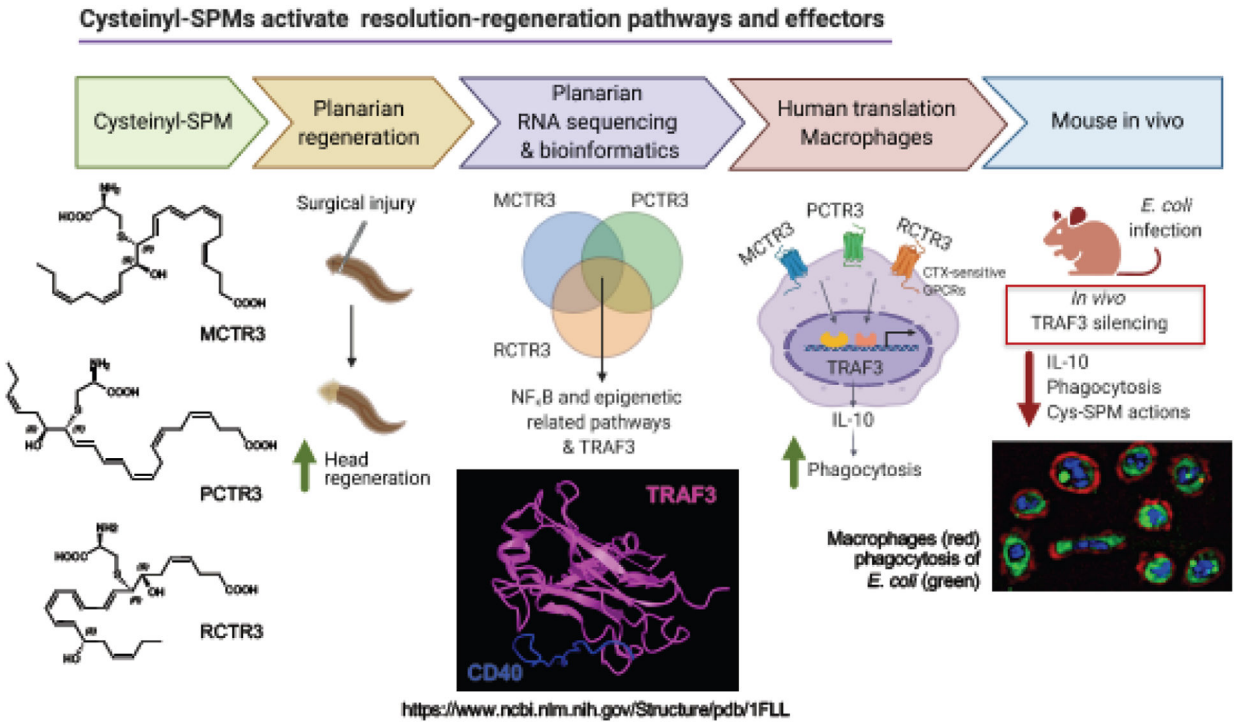


Figure 6. cys-SPMs activate resolution-regeneration pathways and effectors

Using planaria as a model organism with RNA-seq, cys-SPM-activated pathways were identified during regeneration including TRAF3, which contributes to cys-SPM's pro-resolving programs in human macrophage and in mouse E. coli infection.

Table 1(A)

Endogenous SPM production in human tissues: Identification and quantification by mass spectrometry[*,^]

Tissue/organ	SPM	Quantities	Reference
Serum	Tuberculosis and Type 2 diabetes		[104]
Lymph nodes	MCTR1–3, PCTR1–3	1–5 pg/500 mg protein	[76]
Spleen	MCTR1, MCTR2, PCTR1,	1–5 pg/500 mg protein	[76]
	RCTR1–3	60–400 pg/500 mg protein	
Brain	MCTRs, PCTRs, RCTRs	1–5 pg/500 mg protein	[76]
Plasma	$RvD_{n\text{-}3\ DPA}$	10–30 pg/ml	[105]
	RvEs, RvDs, PD1, MaR1 (Type 2 diabetes mellitus)	30–190 pg/ml	
	MaR1, RvD2, RvD4, RvD5 (adolescents)		[106]
	RvE1 RvD1, RvD5	2–22 pg/ml	[101]
Cerebrospinal fluid	RvT2, RvT4 (Tuberculous meningitis)	1–2 pg/ml	[107]
	RvD1, RvD5 PD1 (multiple sclerosis)	0.02–0.68 pg/ml	[108]
Synovial fluid	PD1, RvD1, RvD2, RvD5, MaR1 (RA & OA)	~5 pmol/ml	[109]
Bone marrow	RvD4		[110]
	MCTR1	6 pg/4 ml	[76]
	RCTR1–3	24–180 pg/4 ml	
Blister	RvD1, RvD3	10–15 pg/ml	[111]
Vagus nerve (Electric stimulation)	RvE1–3, RvD3–6, NPD1/PD1, MaR1	1–40 pg/3.5 cm of tissue	[39]
Metabolic syndrome (weight loss program)	RvE1, RvE3, RvD2, MaR1 (Neutrophils ex vivo)	26–1340 pg/4.5 × 10^6 PMN	[112]
Obesity	RvD1–6, MaR1, MaR2, PD1, RvEs (Plasma and leukocytes)	0.2–200 pg/ml plasma, 0.1–2 pg/3×10^6 cells	[113]
Stenotic aortic valves	RvE1, RvD3	~500 – 3500 pg/g tissue	[114]
Sputum (Cystic fibrosis)	RvD1	~200 pg/ml	[115]
Nonobstructive coronary artery disease (WARRIOR) trial	RvD1, RvD2, RvD3, RvD5, RvE1, MaR1, 18-HEPE		[40]
Chronic rhinosinusitis	RvD1, RvD2, LXA_4		[116]
Bariatric surgery	RvD3, PD1, MaR1, 17-HDHA, 14-HDHA		[117]

Table 1(B)

Omega-3 supplementation increases SPMs in humans

Diseases/conditions	Doses and regimen	SPM present	SPM 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	[118]
Effect of n-3 in pregnancy on offspring	n-3 PUFA; 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	[119]
Healthy individuals (Serum & plasma)	ω-3 ethyl esters; 4 g/day; 8–12 wks	RvE1, RvD1, 17-HDHA, 18-HEPE (plasma and serum)	RvE1, RvD1, 17-HDHA, 18-HEPE	[120]
Peripheral artery disease (OMEGA-PAD II trial)	n-3 PUFA; 4.4 g/day; 3 months	RvE1, RvE2, RvE3 (plasma)	RvE3	[121]
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	[122]
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, $RvD_{n\text{-}3\ DPA}$, $PD_{n\text{-}3\ DPA}$, MaRn-3 DPA	[123]
Arthritis	Microalgae oil (Schizochytrium sp); 2.1 g DHA/day; 10 wks	14-HDHA, 17-HDHA (plasma)	14-HDHA, 17-HDHA	[124]
Coronary artery disease	EPA and DHA, 3.36 g daily	RvE1, MaR1, 18-HEPE		[125]
Pregnant women (Umbilical cord blood)	EPA-rich fish oil (1060 mg EPA plus 274 mg DHA), or DHA-rich fish oil (900 mg DHA plus 180 mg EPA)	17-HDHA, 14-HDHA		[126]

*These tables report publications in the period of 2017–2021 that confirm and extend original findings (reviewed and references in [5]).

^For human trial publications on resolvins, please see https://pubmed.ncbi.nlm.nih.gov/?term=Resolvin&filter=pubt.clinicaltrial&sort=date

Table 2.

SPM receptor-dependent functions

SPM Receptor	Genetic modification or pharmacological intervention		Reference
RvE1 receptor [ChemR23]	Transgenic mice	↑ RvE1 action limiting PMN ↑ Phagocytosis of P. gingivalis ↓ Bone loss	[127]
	Knockout mice	↑ Proatherogenic signaling in macrophages, ↑ Increased atherosclerotic plaque size and necrotic core ↓ Phagocytosis	[128]
		↑ Disease progression in Aortic valve stenosis ↓ Beneficial effects of Fat-1^{tg}	[114]
		↓ RvE1 control of hepatic transcriptional profile related to glucose homeostasis, insulin sensitivity, and inflammation	[129]
Leukotriene B4 receptor [BLT1]	Knockout mice	↓ RvE1 regulation of PMN	[130]
	BLT1 antagonist	↓ RvE1-stimulated epithelial wound healing	[131]
RvD1 receptor [ALX]	Transgenic mice	↑ RvD1 action regulating PMN, miRNAs and cytokines	[132]
	Knockout mice	↓ LXA_4 and RvD1 actions limiting peritonitis	[132]
		↓ RvD1 regulation of macrophage transcriptional program of a pro-revascularization phenotype	[133]
		↓ RvD1 protection of post-transplant lung ischemia-reperfusion injury	[134]
RvD1 receptor [GPR32]	shRNA silencing of GPR32	↓ Phagocytosis and efferocytosis	[135]
		↓ RvD1 pro-resolving actions in primary human macrophages	[136]
	Transgenic/Knock-in	↑ AT-RvD1 functions in macrophage phagocytosis and intracellular signaling	[137]
RvD2 receptor [GPR18]	Knockout mice	↓ RvD2-accelerated resolution of infection and organ protection	[138]
		↓ RvD2 protective actions in CLP/sepsis	[139]
		↓ RvD2-enhanced re-epithelialization in skin injury	[140]
		↓ RvD2 action in reducing tumor burden	[141]
		↓ RvD2 regulation of the Akt-1 pathway in myoblasts, RvD2 targets muscle stem cells, leading to increased myogenesis, providing a new therapeutic approach for Duchenne muscular dystrophy	[142]
	Myeloid KO	↑ Steatosis and hepatic fibrosis ↓ RvD2-enhanced phagocytosis with bone marrow macrophages	[143]
	siRNA	↓ RvD2's ability to increase myotube fusion and growth	[142]
	GPR18 Antagonist	↓ RvD2 protective actions in MCAO/R-induced brain injury	[144]
		↓ RvD2 analgesic action in inflammatory bowel syndrome	[145]
		↓ RvD2 analgesic action in bladder pain	[146]
		↓ RvD2-reduced atherosclerosis and necrotic core area	[147]
		↓ RvD2-enhanced macrophage phagocytosis	
MaR1 receptor [LGR6]	siRNA silencing of LGR6	↓ MaR1 functions in increasing cAMP, macrophage phagocytosis and efferocytosis, CREB phosphorylation	[148]
		↓ MaR1 actions in vivo in reducing PMN and stimulating phagocytosis	
		↓ MaR1-dependent protection in AAA formation and SMC α-actin expression	[149]

SPM Receptor	Genetic modification or pharmacological intervention		Reference
		↓ MaR1-alleviated high glucose-induced inflammation	[150]
		↓ MaR1-inhibited smooth muscle proliferation	[151]
		↓ MaR1-promoted apoptosis	
		↓ MaR1-increased cAMP in osteoblasts	[152]
		↓ MaR1 protection of post-transplant lung ischemia-reperfusion injury	[134]
	Overexpression	↑ MaR1-increased cAMP in osteoblasts	[152]
	Knockout mice	↓ Osteoblast proliferation, differentiation, and mineralization	[152]
		↓ MaRI's protective signaling in respiratory syncytial virus-induced lung inflammation	[153]
PD1 receptor [GPR37]	Knockout	Delayed resolution of inflammatory pain	[154]
		↓ Macrophage phagocytic activity	
		↓ PD1 protective actions in sepsis induced by LPS and Listeria	[155]

Table 3.

Stereochemical Assignment names and IDs of cys-SPMs

cys-SPMs	Chemical names	Reference	*Lipid Maps LM ID	**PubChem CID
MCTR1	13R-glutathionyl-14S-hydroxy-4Z,7Z,9E,11E,16Z,19Z-docosahexaenoic acid	[156]	LMFA04050005	122368871
MCTR2	13R-cysteinylglycinyl-14S-hydroxy-4Z,7Z,9E,11E,16Z,19Z-docosahexaenoic acid	[156]	LMFA04050006	122368872
MCTR3	13R-cysteinyl-14S-hydroxy-4Z,7Z,9E,11E,16Z,19Z-docosahexaenoic acid	[156]	LMFA04050007	122368873
PCTR1	16R-glutathionyl-17S-hydroxy-4Z,7Z,10Z,12E,14E,19Z-docosahexaenoic acid	[157]	LMFA04040004	132472316
PCTR2	16R-cysteinylglycinyl-17S-hydroxy-4Z,7Z,10Z,12E,14E,19Z-docosahexaenoic acid	[158]	LMFA04040005	132472317
PCTR3	16R-cysteinyl-17S-hydroxy-4Z,7Z,10Z,12E,14E,19Z-docosahexaenoic acid	[158]	LMFA04040006	132472318
RCTR1	8R-glutathionyl-7S,17S-dihydroxy-4Z,9E,11E,13Z,15E,19Z-docosahexaenoic acid	[76]	LMFA04030014	132472320
RCTR2	8R-cysteinylglycinyl-7S,17S-dihydroxy-4Z,9E,11E,13Z,15E,19Z-docosahexaenoic acid	[76]	LMFA04030015	132472321
RCTR3	8R-cysteinyl-7S,17S-dihydroxy-4Z,9E,11E,13Z,15E,19Z-docosahexaenoic acid	[76]	LMFA04030016	132472322

This table is an update from [5]

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

** https://pubchem.ncbi.nlm.nih.gov/

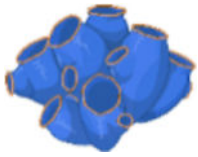
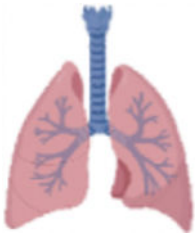
Table 4.

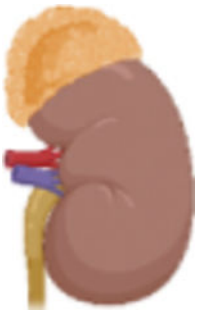
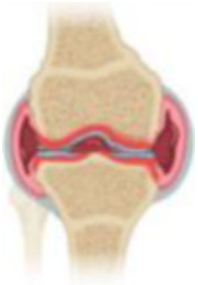
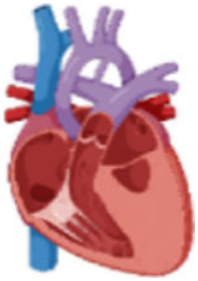
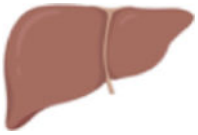
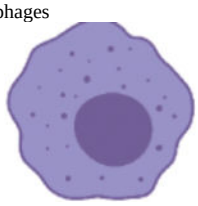
Endogenous cys-SPM production from planaria, mouse to human

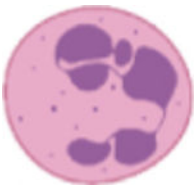
Species	Cellular or in vivo systems	Cys-SPMs	Reference
Planaria	Regeneration	MCTR1, MCTR2	[75]
Mouse	Peritoneal exudates (E. coli)	PCTR1, PCTR3	[33]
	Spleen (E. coli peritonitis)	PCTR1, PCTR3	
	Skin (S. aureus infection)	PCTR1	[83]
	Lung (allergic inflammation)	MCTR1–3	[80]
	Lung (RSV infection)	PCTR1	[84]
Pig	Periodontal ligament stem cells	MCTR3	[78]
Human	Brain	MCTR1–3, PCTR1–3, RCTR3	[76]
	Spleen	MCTR1,2, PCTR1, RCTR1–3	
	Lymph node	MCTR1–3, PCTR1–3, RCTR3	
	Bone marrow	MCTR1, RCTR1–3	
	Lungs	MCTR1–3	[80]
	Macrophages	MCTR1–3, PCTR1–3, RCTR1–3	[33]
	M2 macrophages	PCTRs	[77]
	Platelets	MCTRs	[77]
	Joints (arthritis)	MCTR1–3	[159]

Table 5.

cys-SPM functions: independent confirmations

Species	In vitro or in vivo	Cys-SPMs	Actions	Reference
Dugesia japonica 	Head regeneration	MCTRs, PCTRs, RCTRs	Accelerate head regeneration	[75]
				[76]
		MCTR3, PCTR3, RCTR3	Gene regulation	[86]
Ciona intestinalis 	Heartbeats	MCTRs	Block LTD_4-stimulated negative inotropic action	[79]
Mus musculus 	E. coli peritonitis	MCTRs	Accelerate resolution of infection	[75]
		PCTR1		[157]
		RCTRs		[76]
	Hind-limb	MCTR1, MCTR2	Reduce lung tissue damages	[75]
	Ischemia-reperfusion	RCTRs	Limit reflow organ injury	[76]
	Allergic airway inflammation	MCTRs	Promote resolution of allergic airway responses	[80]
				[82]
	Respiratory Syncytial Virus pneumonia	PCTR1	Decrease viral load and leukocytes	[84]
	Bacteria pneumonia and viral Infection	MCTRs	Decrease lung inflammation and bacterial load	[67]
	Acute lung injury	MCTR1, RCTR1	Improves alveolar fluid clearance	[160, 161]
		MCTR1, PCTR1	protects lung endothelial glycocalyx	[162, 163]
		MCTR3	Reduces leukocytes and edema	[164]
	ARDS	PCTR1	Improves pulmonary edema fluid clearance	[165]
	Lung fibrosis		Attenuates lung inflammatory and fibrotic response	[166]
	Infectious skin wound	PCTR1	Stimulates wound closure. Reduces bacterial titers.	[83]

Species	In vitro or in vivo	Cys-SPMs	Actions	Reference
	Septic Kidney injury	MCTR1	Suppresses ferroptosis	[167]
	Arthritis	MCTR3	Pro-resolving and tissue protective	[159]
	Cardiac injury	MCTR1	Improves mitochondrial biogenesis Reduces IL-17A, enhances cardiac function	[168, 169]
	Hepatic ischemia-reperfusion	MCTR1	Inhibits ferroptosis by promoting Nrf2	[170]
Sus domesticus 	Periodontal stem cells	MCTR3	Reduces proinflammatory cytokines	[78]
Homo sapiens 	Macrophages 	MCTRs, PCTRs, RCTRs	Stimulate phagocytosis, efferocytosis and intracellular ROS	[75, 76, 79]

Species	In vitro or in vivo	Cys-SPMs	Actions	Reference
		MCTR3, PCTR3, RCTR3	Increase TRAF3, IL-10, cAMP	[86]
	Macrophages and monocytes	PCTR1	Enhances chemotaxis and adhesion	[75]
	PMN 	MCTRs, PCTR1	Stimulate phagocytosis and intracellular ROS	[75, 157]
		RCTRs	Reduces chemotaxis and adhesion	[76]
	Keratinocyte 	PCTR1	Promote migration	[83]
	Precision-cut lung slices	MCTR3	blocks LTD_4-initiated airway contraction	[80]
	bronchial epithelial cells	PCTR1	Increases IFN-lambda expression	[84]