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Review

E-series resolvins metabolome, biosynthesis and critical role of stereochemistry of specialized pro-resolving mediators (SPMs) in inflammation-resolution: Preparing SPMs for long COVID-19, human clinical trials, and targeted precision nutrition

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ABSTRACT

The COVID-19 pandemic has raised international awareness of the importance of rigorous scientific evidence and the havoc caused by uncontrolled excessive inflammation. Here we consider the evidence on whether the specialized pro-resolving mediators (SPMs) are ready to meet this challenge as well as targeted metabolomics of the resolution-inflammation metabolomes. Specific stereochemical mechanisms in the biosynthesis of SPMs from omega-3 essential fatty acids give rise to unique local-acting lipid mediators. SPMs possess stereochemically defined potent bioactive structures that are high-affinity ligands for cognate G protein-coupled surface receptors that evoke the cellular responses required for efficient resolution of acute inflammation. The SPMs biosynthesized from the major omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are coined Resolvins (resolution phase interaction products; E series and D-series), Protectins and Maresins (macrophage mediators in resolving inflammation). Their biosynthesis and stereochemical assignments are established and confirmed (>1,441 resolvins publications in PubMed.gov) as well as their functional roles on innate immune cells and adaptive immune cells (both lymphocyte T-cell subsets and B-cells). The resolution of a protective acute inflammatory response is governed mainly by phagocytes that actively clear apoptotic cells, debris, blood clots and pathogens. These resolution phase functions of the acute inflammatory response are enhanced by SPMs, which together prepare the inflammatory loci for homeostasis and stimulate tissue regeneration via activating stem cells and the biosynthesis of novel cys-SPMs (e.g. MCTRs, PCTRs and RCTRs). These cys-SPMs also activate regeneration, are organ protective and stimulate resolution of local inflammation. Herein, we review the biosynthesis and functions of the E-series resolvins, namely resolvins E1 (the first n-3 resolvins identified), resolvins E2, resolvins E3 and resolvins E4 biosynthesized from their precursor eicosapentaenoic acid (EPA), and the critical role of total organic synthesis in confirming SPM complete stereochemistry, establishing their potent functions in resolution of inflammation, and novel structures. The physical properties of each biologically derived SPM, *i.e.*, ultra-violet (UV) absorbance, chromatographic behavior, and tandem mass spectrometry (MS²) fragmentation, were matched to SPMs biosynthesized and prepared by stereospecific total organic synthesis. We briefly review this approach, also used with the endogenous D-series resolvins, protectins and maresins confirming their potent functions in resolution of inflammation, that paves the way for their rigorous evaluation in human tissues and clinical trials. The assignment of complete stereochemistry for each of the E and D series Resolvins, Protectins and Maresins was a critical and required step that enabled human clinical studies as in SPM profiling in COVID-19 infections and experimental animal disease models that also opened the promise of resolution physiology, resolution pharmacology and targeted precision nutrition as new areas for monitoring health and disease mechanisms.

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1. Introduction

The current pandemic and COVID-19 infections have painfully underscored the important contribution of excessive, uncontrolled inflammation and collateral tissue damage to disease pathology that can amplify inflammation and lead to untimely death of patients [1,2]. The acute inflammatory response is an essential and temporal process evoked in the host defense of infection as well as by tissue injury that normally is self-limited and resolves to return to tissue homeostasis on its own [3,4]. In the acute inflammatory response, human phagocytes, both neutrophils and macrophages, play central roles in host defense and produce endogenous lipid mediators (LMs), e.g. eicosanoids such as prostaglandins and leukotrienes, that are potent pro-inflammatory mediators critical to host defense [5,6]. The acute inflammatory response is functionally characterized in two separate and discrete phases, the initiation phase (Fig. 1A) and resolution phase [7–9]. Mediators such as complement components, chemokines and cytokines have well appreciated roles in the initiation phase of the acute inflammatory response summoning neutrophils to the local site(s) of invasion or tissue injury [10] as do lipid mediators derived from the precursor arachidonic acid [6,7]. In the initiation phase, prostaglandins such as PGE₂ regulate the cardinal signs of inflammation: local capillary blood flow, heat, swelling and pain [7]. At sites of inflammation-resolution, physiologic hypoxia is transient in the local milieu that was modeled and played a triggering role in our original studies [7,8] on the biosynthesis and functions of the resolvins (*vide infra*). In our studies on the resolution phase of acute inflammation in self-limited or self-resolving acute inflammation [7], infection [11], and collateral organ damage [4], a novel superfamily of potent endogenous LMs emerged, which one of the authors coined specialized pro-resolving mediators (SPMs: resolvins, maresins, protectins and lipoxins, derived from the major essential omega-3 polyunsaturated fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) that were first uncovered in mouse resolving inflammatory exudates), given the potent and special functions *in vivo* of this superfamily of mediators [7]. These inflammatory exudates (*i.e.*, pus) were temporally interrogated along the time course and were comprised of a mixture of leukocytes recruited *in vivo* to form the exudates [8,12,13]. Each family of mediators was named given their potent bioactivity and unique structures [7,8,14,15]. The biosynthesis of the SPMs was investigated in detail and confirmed with isolated human leukocytes. SPMs play a fundamental role in the resolution of acute inflammation by governing the temporal and spatial regulation of neutrophil traffic and down regulation of the pro-inflammatory mediators, e.g., eicosanoids, cytokines, and chemokines [7]. By their defined criteria as a pro-resolving molecule as originally proposed [7,8], each SPM specifically limits further neutrophil infiltration to the site and enhances the clearance of apoptotic cells by macrophages, reduces both cytokine and eicosanoid storms, reduces pain (Fig. 1A) and shortens the resolution interval *in vivo* [4,7,12,16]. Macrophages play a central function in the resolution phase of inflammation by actively clearing dead cell debris, apoptotic neutrophil cells [16] and biosynthesizing distinct families of LMs that are dependent on the macrophage phenotype [17,18]; see Fig. 1. The mediators biosynthesized by macrophages are either pro-inflammatory or anti-inflammatory-pro-resolving depending on the specific macrophage agonists and the availability of the required precursor [18,19]. In this context, human macrophages incubated with the high-mobility group box 1 protein (HMGB1) stimulate the production of pro-inflammatory cytokines and leukotrienes, whereas the high-mobility group box 1 protein (HMGB1) exposed together with the complement component 1q (C1q) switches these macrophages to produce SPMs [20]. Apoptotic PMN, M2 macrophages and microglial cells are major human cell types that produce and release SPMs [17,18] (Fig. 1B). Human PMN also biosynthesize resolvins *via* transcellular biosynthesis routes when interacting with vascular endothelial cells or mucosal epithelial cells (e.g., lung airway, gastrointestinal tract) [8,13,21,22].

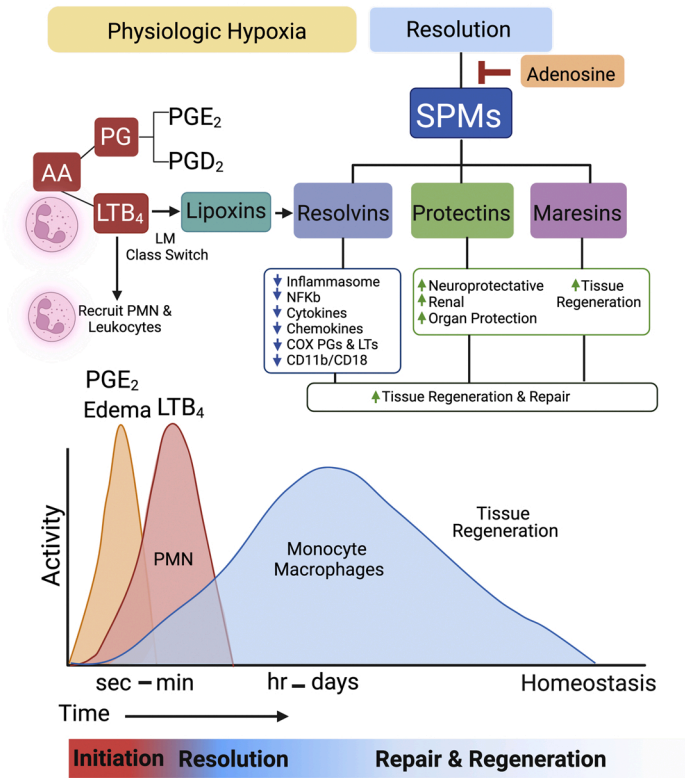
2. SPMs in COVID-19 infections and other human studies

The stereochemical assignments of each of the SPMs originally reported by the Serhan Lab (reviewed herein) permitted SPM identification by other research teams in COVID-19 patients (Table 1) along with eicosanoids, *i.e.*, prostaglandins and leukotriene [23–26]. New rigorous LC-MS-MS-based profiling methods introduced using synthetic SPM [27], internal standards (for some of the original publications, see Refs. [28–30]) helped to establish criteria for endogenous production and identification of resolvins in tissues enabling the recent publications from independent laboratories with human subjects providing results (Table 1) suggesting that, in COVID-19 infections, endogenous SPM production is dysregulated *in vivo* during these viral infections [23,31]. Each of these studies used LC-MS-MS-based identification enabled by the availability of synthetic SPMs and deuterium-labeled internal standards that were first introduced by the Serhan laboratory (reviewed in Ref. [27]). SPMs are now commercially available from several sources based on our original studies determining the stereochemical assignments of each SPM with human leukocyte, mouse exudates and tissues reviewed here and accomplished with support from NIH Program Project grant P01GM095467 to the CN Serhan research team.

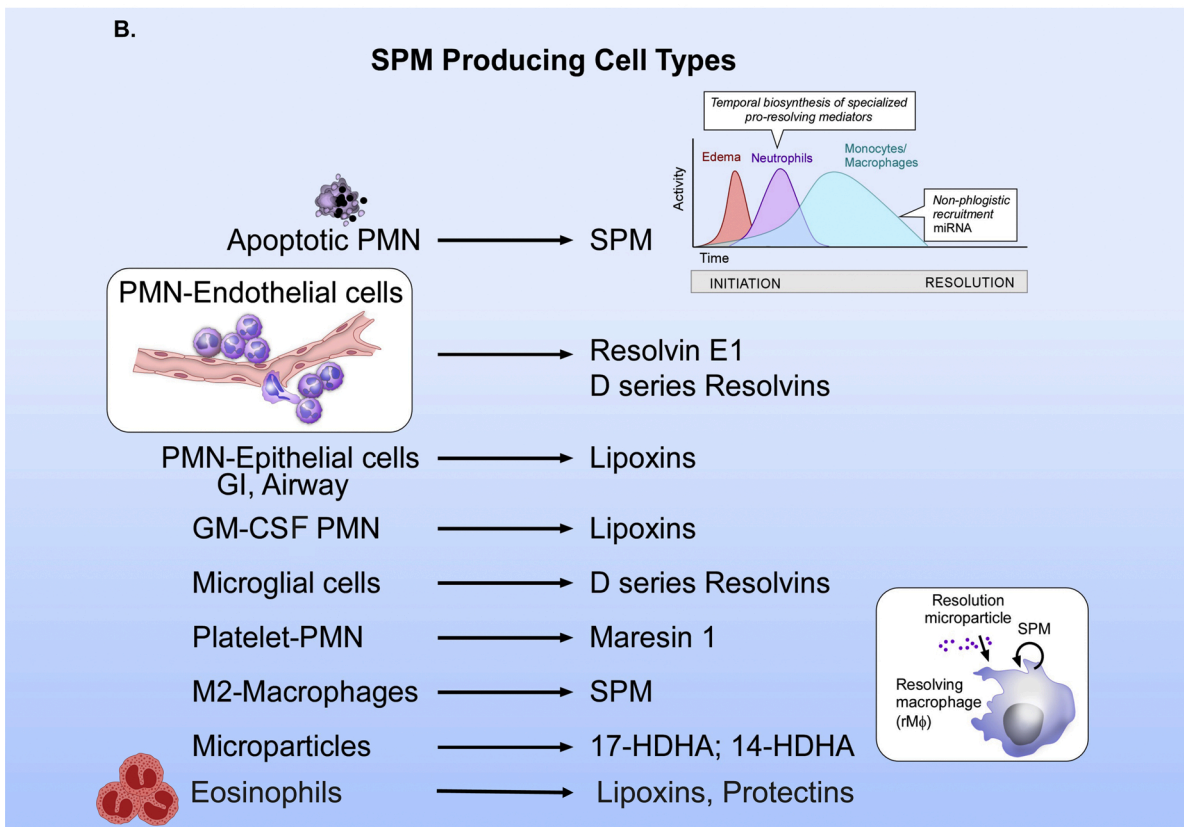
In most COVID-19 infection studies, there appears to be an excess of proinflammatory lipid mediators PGs and LTB₄ with diminished amounts of SPMs compared to peripheral blood of control subjects (Table 1). The increase in pro-inflammatory eicosanoids may drive as well as amplify the uncontrolled cytokine storms and excessive lung inflammation that possibly reflect systemic inflammation characteristic of COVID-19 infections [32,33]. In one published study analyzing bronchial alveolar lavage fluids from COVID-19 patients, in addition to eicosanoids such as leukotrienes and prostaglandins, the COVID-19 lung lavages (Table 1) contained high amounts of resolvins and lipoxins [23]. Given the potent pro-resolving functions of these SPMs, it appears that in this study endogenous SPM produced *in vivo* that appear in BAL were functionally unable to counteract the excessive pro-inflammatory phenotype in COVID lung infections and/or were unable to engage leukocytes to activate the endogenous resolution response needed in these patients. Much still needs to be learned about the potential role of specific SPMs in COVID-19 infections during the time course of human infection and disease. Recent *in vitro* studies demonstrated that both Resolvin D1 and Resolvin D2 each are potent in reducing human macrophage production of pro-inflammatory cytokines and chemokines in response to the virus spike protein [34]. It is appropriate to emphasize that these early fundamental studies are vital to understanding the pathogenesis of COVID-19 infections and the potential role of lipid mediators that could give useful new directions for treatments of COVID-19, long COVID and in lasting immunity. These new findings (Table 1) and many other human studies for SPMs from international experts [35–55] would not have been possible without the i) complete stereochemical assignments of each of the potent bioactive SPMs produced by human and mouse leukocytes, ii) their biosynthesis from n-3 essential fatty acids (EPA and DHA) and iii) total organic synthesis with rigorous matching studies with endogenous SPMs along with our dedicated and talented organic chemistry collaborators summarized herein. In this relatively new SPM field, the Serhan lab has collaborated for many years with Professor Nicos Petasis and colleagues as part of the total synthesis core of our NIH-supported Program Project grant P01GM095467, Professor Trond Hansen and team in Oslo, Norway [56], Professor Bernd Spur and Anna Rodriguez [57–59], and the organic synthesis group at Cayman Chemical; for examples, see the custom synthesis of benzo-RvD1 analog mimetic [60] and the new RvE4 [61].

Importantly, the many other elegant human studies on SPMs would not have been possible without reliance on the complete stereochemically defined synthetic SPMs and their internal standards for LC-MS-MS-based analyses with adult tissues [35–55] and adolescent human peripheral blood samples [38] as well as their scale-up for commercial availability [62]. A recent clinical trial reported that local topical

A.



B.



(caption on next page)

Fig. 1. Schematic illustration of the acute inflammatory response with the strategic positions of lipid mediators in this local protective response.

Panel A: Initiation of the acute inflammatory response ideally proceeds to complete resolution and homeostasis. Edema, regulated by PGE₂ in seconds to minutes, enables neutrophil tissue/exudate influx by chemotaxis to the arachidonic-acid-derived leukotriene B₄ (LTB₄). The prostaglandins PGE₂ and PGD₂ activate the lipid mediator class switch [13], triggering the increase in 15-lipoxygenase [211] that leads to production of lipoxins starting the decrease in neutrophil numbers in the inflammatory exudate and beginning the resolution phase and biosynthesis of resolvins [8,21], protectins, and maresins (the SPM), which carry functions critical to timely resolution and homeostasis [4]. These include limiting further PMN recruitment to the site and the uptake and removal of apoptotic PMN and cell debris by macrophages. The resolvins down regulate and counteract the cytokines, chemokines, and eicosanoids, e.g., prostaglandins and leukotrienes, the pro-inflammatory signals produced *via* inflammasomes, and NF-κB are reduced and cellular adhesion molecules C11b/CD18 are also downregulated. The production of protectins and maresins from DHA is organ protective and activates tissue regeneration as needed to repair the injured site for homeostasis (see text for further details). Adenosine blocks the biosynthesis of SPMs from omega-3 fatty acids [194], illustrating that there are many checkpoint regulators involved in the resolution of the acute inflammatory response and the resolution of this complex leukocyte trafficking event that is critical to host defense, elimination of invading bacteria, and survival. Each SPM reduces proinflammatory mediator production and expression as well as enhances PMN and macrophage-mediated bacterial phagocytosis and killing.

Panel B: SPM-producing cell types. Apoptotic PMN, brain microglial cells and M2 macrophages biosynthesize SPM from the single cell type, while intact neutrophil and vascular endothelial cells biosynthesize SPM *via* transcellular biosynthesis (see text for details and original references; for example, see Fig. 3). Eosinophils are a source of SPM, lipoxins, and protectins and are rich in 15-lipoxygenase [209,212], giving a new role for these cells in resolution and wound healing *via* their production of SPM.

Table 1

Resolvins*, SPMs and Eicosanoids in Human Subjects with COVID-19 Infections.

Reference	Findings	Source
Schwarz et al. [31]	Dysregulation of eicosanoids increases 5-lipoxygenase, leukotriene, prostaglandins, EETs, specific resolvins in severe illness, decreases 12-LOX (ALOX12) and COX-2; immune lipid mediator metabolome imbalance in severe COVID-19	Serum
Archambault et al. [23]	Predominance of prostaglandins, thromboxane, LTB ₄ and leukotrienes; increased lipoxin A ₄ and D-series resolvins	Bronchoalveolar lavages (BAL)
Koenis et al. [25]	Proinflammatory eicosanoids and SPMs were elevated in COVID-19 BAL	
Turnbull et al. [26]	Disrupted resolution and altered phagocyte responses	Plasma
Arnardottir et al. [195]	SPM and eicosanoid metabolomes identified in critically ill COVID-19 showing dysregulation during infection	
	Omega-3 in resolution of COVID-19; randomized clinical trial	COVID-Omega-F

* The potential for resolvins and other SPMs as new therapeutic approaches in the resolution of inflammation was recognized early by inflammation experts [196] from the time of their initial discovery; see [197].

treatment of gingival inflammation with a proresolving lipoxin/resolvin stable analog is safe and effective as well as activated endogenous production of SPMs present in peripheral blood [63]. A new generation of lipoxin stable analog mimetics introduced by investigators in Dublin hold exceptional promise for novel pro-resolving treatments in inflammation-resolution for kidney diseases and the many diabetic complications [64–66]. They demonstrated with analyses of nasal lavages that SPMs, e.g., RvD2, are dysregulated in human rhinosinusitis. This may be an indication where treatment with a pro-resolving molecule can be a useful new treatment approach [67].

3. E series Resolvins (resolution phase interaction products) and new bioactive members: stereochemistry

In the original studies from the Serhan lab, eicosapentaenoic acid (EPA) was found to be the obligatory precursor to the first resolvins, namely resolvin E1 [21] and the E-series resolvins biosynthesis [8]. Resolvin E1 is produced *via* transcellular biosynthesis with interactions between human neutrophil (PMN) and hypoxic vascular endothelial cells that release 18-HEPE, which is converted to the bioactive resolvin E1 [21] (Fig. 2). The therapeutic uses of EPA in cardiovascular medicine and health are still heatedly debated [68] even today, 50 years after the landmark Greenland study and publication clearly pointing to reduced cardiovascular disease in the indigenous population study participants

and their marine-based nutrition [69]. Prescription omega-3 fatty acids are used clinically to reduce triglycerides in patients. Employing Icosapent ethyl ester of EPA, a human clinical trial with hundreds of subjects enrolled showed a statistically significant reduction in risk of cardiovascular disease (CVD) [70]. The omega-3 essential fatty acids are also being considered in COVID-19 patients with cardiovascular complications as additional therapies in these patients [71]. These are significant advancements for the field of omega-3-based therapeutics given the worldwide unmet medical needs of our times. The mechanism(s) of EPA efficacy in reducing cardiovascular disease remains to be determined and is an ongoing interest of many investigators along with the potential role of the EPA resolution metabolome in the resolution of inflammation in human disease including COVID-19 infections (Table 1).

In our original experiments, we found that hypoxic human vascular endothelial cells converted EPA to a novel 18-hydroxyeicosapentaenoic acid (18-HEPE) that is released from the cells and is precursor for transcellular biosynthesis of resolvin E1 (RvE1) [8,21]. The complete stereochemistry of resolvin E1 was determined, 5S,12R,18R-trihydroxy-6Z,8E,10E,14Z,16E-eicosapentaenoic acid, and its proposed structure and potent bioactions [21] were confirmed with materials prepared by total organic synthesis [21,72]. These matched the products from human neutrophils produced during coincubations with hypoxic endothelial cells and in mouse resolving exudates, given the vast surface area of the vascular endothelium and vessels *in vivo* and high number of circulating PMN that roll on the endothelial surface *in vivo* from head to toe [73]. This is a considerably massive cellular architecture *in vivo* for cell-cell interactions and transcellular biosynthesis of several SPMs [73,74], interactions that can also stimulate resolvin biosynthesis from EPA on command to function on surrounding blood cells [75]. RvE1 is produced *via* transcellular biosynthesis with human neutrophils *via* acetylated cyclooxygenase-2 (COX-2) [21] or the microbial cytochrome P450 [76]. The RvE1 produced *via* co-incubations of human cells matched the properties of the product found in mouse resolving inflammatory exudates and its bioactivity in blocking transmigration and the binding of LTB₄ to its receptor BLT1 [21].

The 18-HEPE released from endothelial cells is converted by the human neutrophil 5-LOX to a 5(6)-epoxide-containing intermediate that was identified by trapping experiments and analyses of the products using both GC-MS and LC-MS-MS as well as derivatives. This 5(6)-epoxide intermediate is converted to RvE1 *via* the LTA₄ hydrolase (LTA₄H) in human neutrophils (see Figs. 3 and 4). This step of the RvE1 biosynthesis was confirmed with human recombinant LTA₄ hydrolase [77,78]. Chiral LC-MS-MS analyses were also carried out with the RvE1 biosynthesis pathway with human leukocytes as well as functional studies with 18S-RvE1 compared directly with RvE1, where both isomers proved to be equally potent with human cells and *in vivo* in mice promoting resolution [77]. Of interest, the 18S-RvE1 isomer is more rapidly inactivated *via* metabolic conversion than RvE1 given the stereoselectivity of the dehydrogenase [77], which may underlie the finding

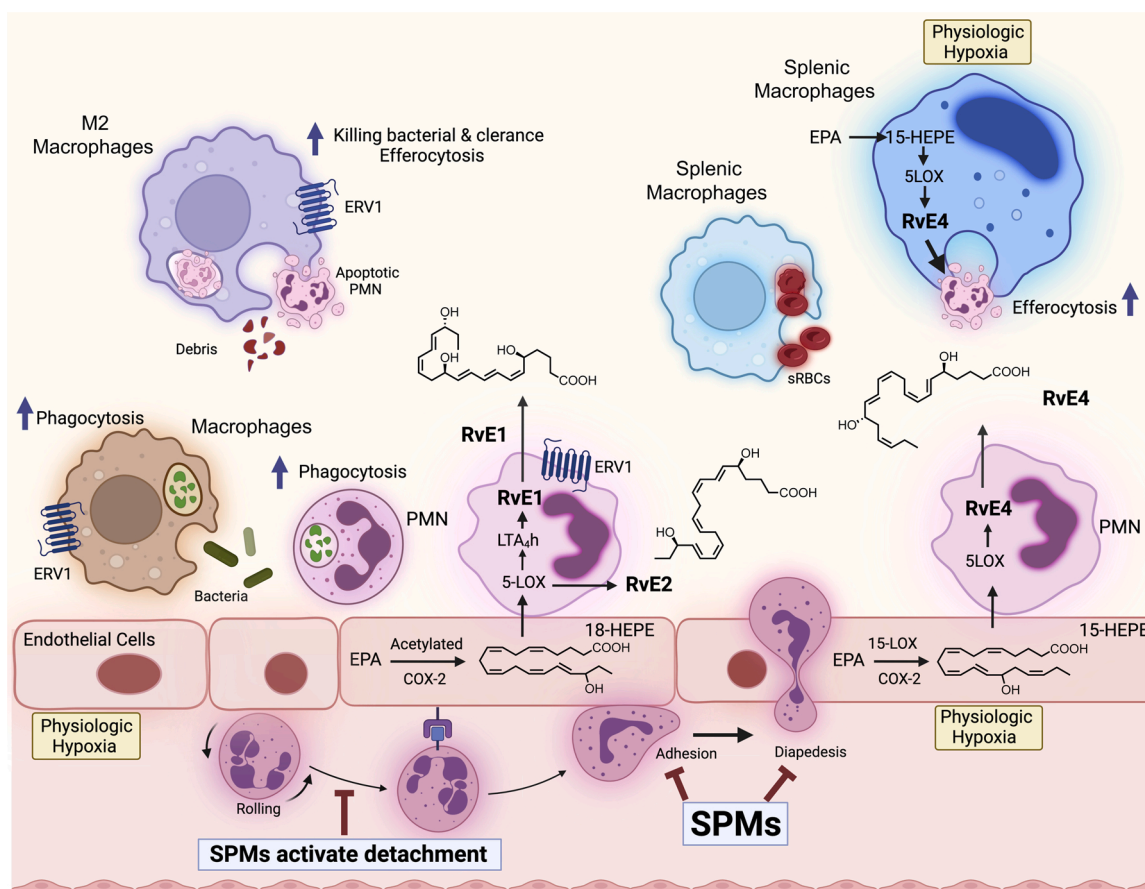


Fig. 2. Schematic illustration of the transcellular and single cell biosynthesis and functions of the E-series Resolvins in efferocytosis, phagocytosis and limiting further PMN infiltration. The transcellular biosynthesis of E-series resolvins involves hypoxic vascular endothelial cells and neutrophils. Physiologic hypoxia activates the conversion of EPA by COX-2 and the upregulation of this enzyme [8,21]. Each SPM limits further PMN recruitment by blocking diapedesis. RvE1 and RvE2 activate specific GPCRs such as ERV1, ChemR23 and BLT1 [72,213].

that RvE1 (which carries its carbon 18 position alcohol in the 18R configuration) is identified *in vivo* using MS^3 with human plasma [72] and in other human studies (*vide infra*).

The biosynthesis of RvE1 [21] from EPA (Figs. 2–4) also yields in this pathway the bioactive resolvin E2 structure 5S,18R-dihydroxy-6E,8Z,11Z,14Z,16E-eicosapentaenoic acid [77,78]; each possesses potent anti-inflammatory-pro-resolving actions. RvE2 is also produced with hypoxic endothelial cells on incubation with human neutrophils [78], and both RvE1 and RvE2 each stereoselectively activate the receptor ChemR23, a G-protein coupled surface receptor [72,77–79]. Anti-ChemR23 (*i.e.*, resolvin E1 receptor) antibodies that activate this RvE1 receptor as an agonist stimulate resolution of inflammation and reduce the cancer burden in mice [79], as does Resolvin E1 and protectin D1 in the activation of endogenous resolution programs *in vivo* [80] in mice and resolvin E1 in rabbits [81], which demonstrates the potential for resolution pharmacology with agonists to control excess inflammation. This principle was also demonstrated (Fig. 5) with metabolically stable analogs prepared for RvE1, 19-phenoxy-paraffluoro-RvE1 [82]. The discovery of agonist antibodies for the proresolving receptors that activate endogenous resolution programs [79] is a very exciting new addition to the potential novel therapeutic approaches to control excessive inflammation and cancer.

Resolvin E3 was the next bioactive mediator to join the E-series of resolvins, discovered by Professor Makoto Arita and his colleagues in Japan. Resolvin E3 proved to have the complete stereochemistry 17R,18R-dihydroxyicoso-5Z,8Z,11Z,13E,15E-eicosapentaenoic acid, containing a vicinal diol that potently blocks neutrophil migration and is biosynthesized *via* the actions of 15-lipoxygenase and confirmed by total

organic synthesis [83]. RvE3 is identified in human tissues *in vivo*, for example in arthritic exudates [46]. The resolvins E1 and RvE2 precursor, 18-HEPE, is a major product of EPA identified in humans *in vivo* (Table 1) that also carries its own bioactivity with potent actions on cardiovascular tissues [84].

Recently, we encountered [85] and elucidated the complete structure [61] of a new bioactive member of the EPA-derived E-series resolvins termed Resolvin E4 (RvE4) given its potent actions and *in vivo* production. The stereochemistry of RvE4 was deduced and the double-bond geometry proposed based on the activity of 15-lipoxygenase (15-LOX) with EPA *via* double lipoxygenation to produce the potent bioactive molecule 5S,15S-dihydroxy-6E,8Z,11Z,13E,17Z-eicosapentaenoic acid. RvE4 is produced in physiologic hypoxia by human neutrophils and macrophages. Given that RvE4 proved to be a potent agonist for efferocytosis of both senescent erythrocytes (sRBCs) and apoptotic neutrophils, it is classified as having resolving functions, and with EPA as the precursor and backbone we grouped it with the E-series resolvins members. This novel bioactive structure was accordingly named RvE4 because it increases the resolution of hemorrhagic exudate *in vivo* in mice [85].

The proposed biosynthesis of RvE4 was recently independently confirmed with purified recombinant human enzymes using 5-lipoxygenase (5-LOX) and 15-LOX with substrate EPA *in vitro* [86]. We establish the complete stereochemistry of RvE4 and its potent functions with isolated human macrophage-mediated efferocytosis employing results from detailed matching experiments [61]. To assign the complete stereochemistry of RvE4 as well as determine whether synthetic RvE4 shares reported physical and biological functions [85], it was deemed

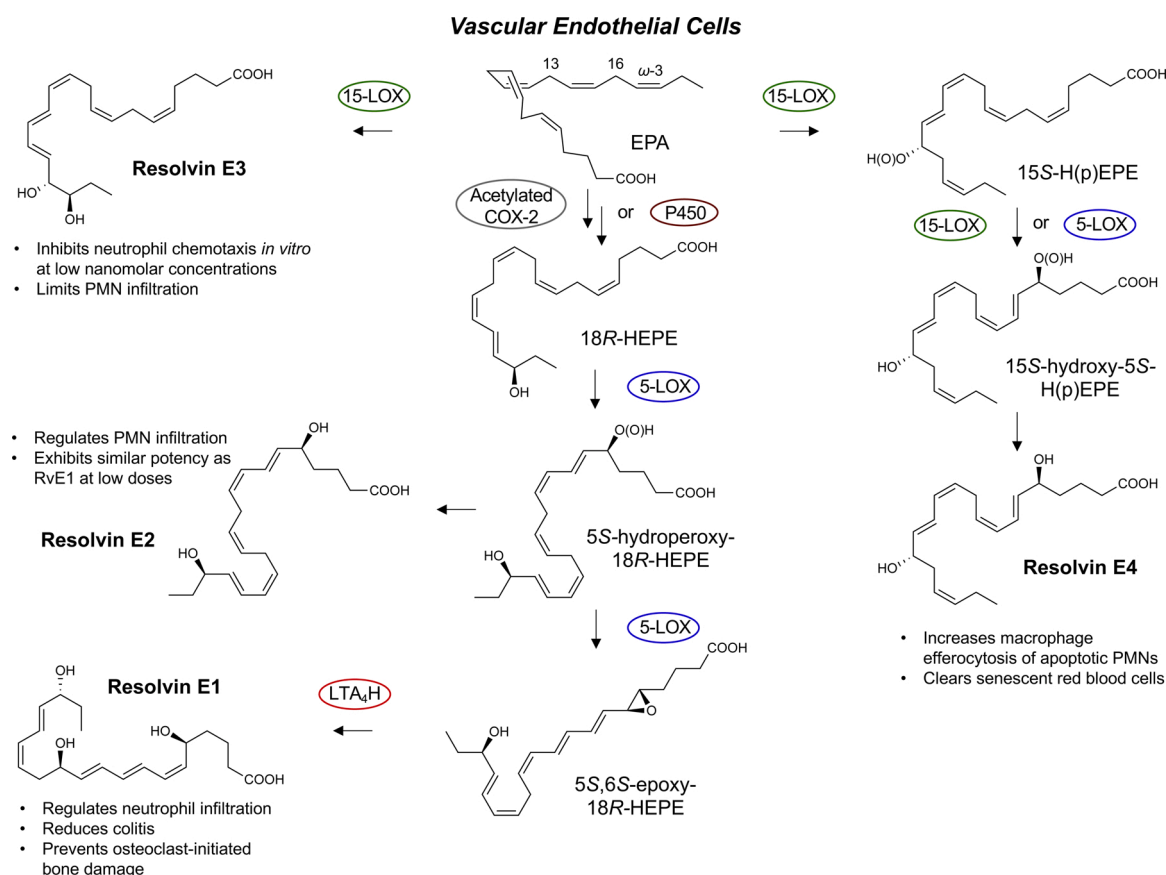


Fig. 3. Proposed Biosynthesis of the E-series Resolvins.

18R-HEPE produced from unesterified EPA *via* acetylated or modified COX-2 as well as p450 [21] is next converted by leukocyte 5-lipoxygenase to the intermediate 5S-hydroperoxy-18R-HEPE, which is either reduced to RvE2 or converted to the epoxide intermediate 5S,6S-epoxy-18R-HEPE to produce RvE1 [77] to carry out their specific functions listed above; see text for details. RvE1 (5S,12R,18R-trihydroxy-6Z,8E,10E,14Z,16E-eicosapentaenoic acid) [8,21,72]. EPA is also a substrate for lipoxygenation by 15-LOX to produce RvE3 (17R,18R-dihydroxy-5Z,8Z,11Z,13E,15E-eicosapentaenoic acid) [83]. Stereochemistry and proposed biosynthetic route of RvE4 are confirmed as well as RvE4's potent actions and functions *in vivo* [61,87].

essential to establish the physical properties of the newly synthesized RvE4 [87].

The structure and stereochemistry of synthetic RvE4 were determined using total organic synthesis from chiral starting materials of known stereochemistry as well as stereocontrolled chemical reactions. This approach was successfully used with each of the potent bioactive SPMs. Synthetic RvE4 was directly compared to the target RvE4 structure that was deduced earlier using the isolated and well-studied 15-lipoxygenase (LOX) enzyme that inserts molecular oxygen into 1,4-cis-pentadienes predominantly in the *S* configuration [85]. Co-injections of biogenic RvE4 with synthetic RvE4 confirmed their identical chromatographic behavior. MS/MS analysis indicated that co-injection gave identical fragmentation with parent ion m/z 333 = M-H and daughter ions at m/z 315 = M-H-H₂O, m/z 271 = M-H-H₂O-CO₂, m/z 253 = M-H-2H₂O-CO₂, m/z 217 = 235-H₂O, m/z 199 = 217-H₂O, and m/z 173 = 235-H₂O-CO₂ essentially identical to that obtained in [61,85,87].

Neutrophils are often the first leukocytes to infiltrate an inflammatory site, recruited from post-capillary venules in large numbers, and therefore their effective removal from the inflammatory site following neutralization of invading microbes is a prerequisite for the resolution of inflammation and return to tissue homeostasis [7,16,88,89]. SPMs, including RvE4, enhance macrophage efferocytosis of apoptotic neutrophils *in vitro* and *in vivo* with both human cells and in murine models of inflammation [7,85]. RvE4 enhanced efferocytosis of sRBCs by M2 macrophages confirming the function of endogenous RvE4 [61]. From results of matching studies using LC-MS-MS, co-elution in LC and fragmentation, UV spectrum absorbance and biological actions, we assigned

the complete double-bond geometry of RvE4, namely 5S,15S-dihydroxy-6E,8Z,11Z,13E,17Z-eicosapentaenoic acid [61,85,87]. Hence, the synthetic RvE4 now commercially available is suitable for use as both a standard for LC-MS-MS-based mediator lipidomics and for further functional investigations. In line with this and of interest, endogenous human RvE4 has already been identified in human cerebrospinal fluid indicating its production *in vivo* in human tissue [90] and is present in plasma obtained from COVID-19 patients [26].

RvE4 was first uncovered from physiological hypoxic triggered biosynthesis of EPA, *via* lipoxygenation, by human macrophages and neutrophils exposed to stimuli [85]. M2 macrophages play critical roles in the resolution of inflammation by virtue of their capacity to carry out efferocytosis [7,16], wound repair [7,91], and production of SPMs [18]. RvE4 proved to be a potent agonist of M2 macrophage efferocytosis of neutrophils: EC₅₀ ~0.23 nM and an EC₅₀ ~0.29 nM for efferocytosis of sRBCs [61]. In human macrophages and neutrophils, RvE4 biosynthesis is solely dependent on the substrate availability, where we found that EPA is released from both phospholipids and triglycerides [85]. EPA is converted by 15-LOX to 15S-HpEPE, which becomes a substrate for further lipoxygenation by either 5-LOX or a second enzymatic turn of 15-LOX to produce 15S-hydroxy-5S-HpEPE; this is further reduced to RvE4 (Figs. 3 and 4). This route of RvE4 biosynthesis by human phagocytes was subsequently also confirmed by Kutzner et al. using recombinant human 5- and 15-LOX co-incubations *in vitro* [86]. EPA is converted by the wild type and recombinant engineered lipoxygenases to double dioxygenation products including RvE4 on a larger synthesis scale [92]. It is likely that the lipoxygenation of EPA is initiated *via*

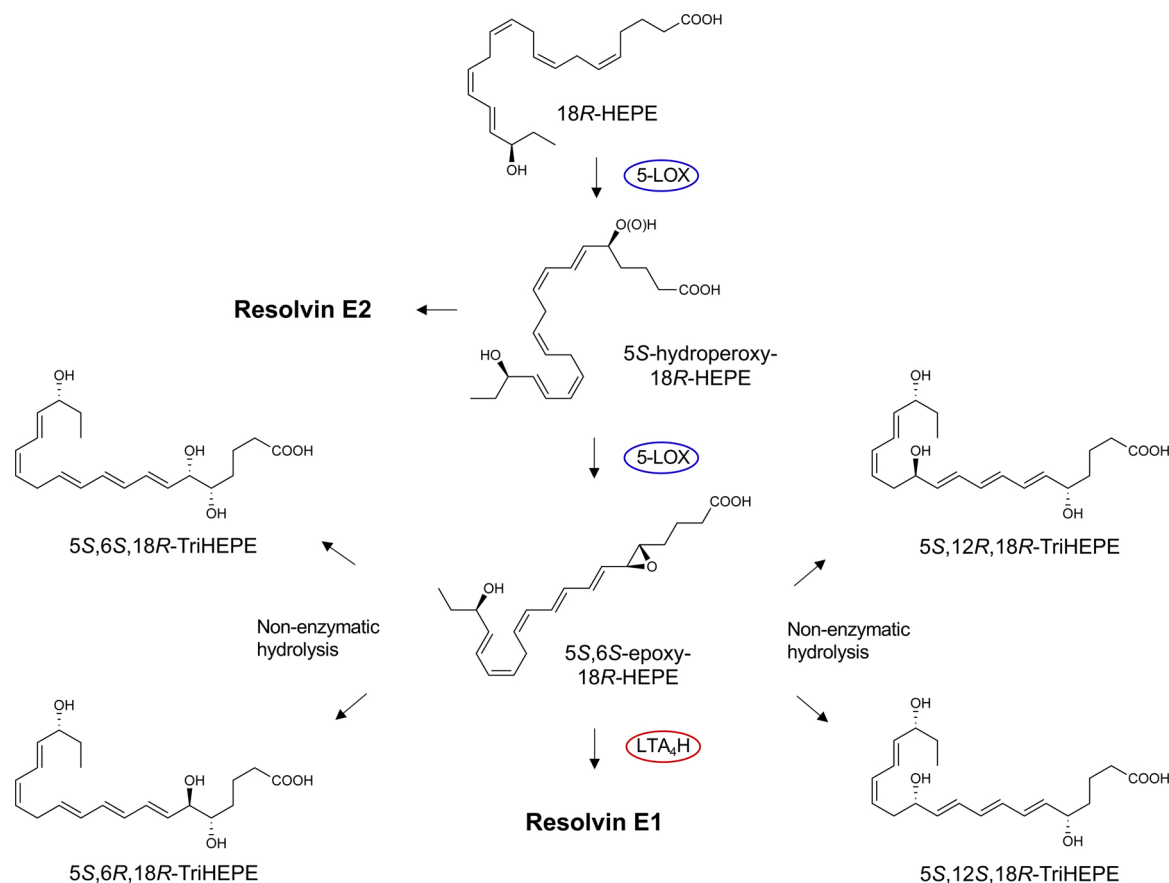


Fig. 4. Biosynthetic Mechanism and Intermediates in Resolvin E1 Production from EPA. The enzymes and structures of 5-LOX and LTA₄H were determined with recombinant enzymes and the 5,6-epoxide intermediate identified by methanol trapping [78]. The biosynthesis of the 18S E-series resolvins and their potent functions were described in [77,78].

hydrogen abstraction at carbon position C7 by 5-LOX to biosynthesize RvE4 in human neutrophils and/or *via* transcellular biosynthesis [21, 93] as depicted in the cellular interactions in Fig. 2 illustration.

Earlier results demonstrated conversion of EPA to 15R-HEPE *via* acetylated COX-2 [21,76]; hence it is likely that this product can be a substrate for lipoxygenation by 5-LOX that can lead to further conversion to the corresponding alcohol giving rise to a novel 15R *epimer* of the RvE4. This 15 *epi*-RvE4 could also be biosynthesized following acetylation of COX-2 by acetyl-CoA and sphingosine *via* sphingosine kinase 1 (SphK1) [94] and/or modified possibly by *S*-nitrosylation of COX-2 [95]. Since 5-LOX has been shown to be phosphorylated to produce 15R-HETE and further converted to 15R-lipoxin A₄ (LXA₄) [96–98], it is likely that, with EPA as a carbon 20:5 substrate like C20:4 arachidonate, phosphorylated 5-LOX can produce 15R-HEPE that can be subsequently converted to the novel 15R-RvE4 structure. Along these lines, RvE4 can be biosynthesized from EPA *via* several separate biosynthetic routes and can now be included in the E-series of pro-resolving mediators; see Table 2. At this juncture, the actions of RvE4 include stimulating human macrophage efferocytosis of apoptotic neutrophils and senescent red blood cells, as well as reducing mouse hemorrhagic exudates by increasing efferocytosis and decreasing neutrophil infiltration *in vivo* [85]. The abilities of RvE4 to limit neutrophil tissue infiltration and to enhance efferocytosis are also functions shared by other SPMs and members of the E-series resolvins (Table 2).

RvE1's pro-resolving actions include stopping neutrophil [21,77,78, 80,99] and dendritic cell migration [72,100], reducing pro-inflammatory cytokines [101], enhancing macrophage phagocytosis and efferocytosis [77,80], enhancing bacterial clearance [101], modulating T cell responses [102] and regenerating periodontal ligament stem cells [103]. RvE1 has unique actions on platelets by inhibiting

adenosine diphosphate (ADP)-activated mobilization of P-selectin to minimize platelet aggregation, which is very useful for prolonged storage of blood that can be useful for needed battlefield transfusions [104]. In addition, RvE1 and the other SPMs have potent actions in the nanogram range *in vivo* that include organ protection, clearing infections (by increasing killing [105]), and stimulating resolution as receptor agonists in, e.g., peritonitis [21,72,77,78,80], sepsis [106], ischemia-reperfusion injury [107], diabetes [108], colitis [99,109,110], lung inflammation [111], obesity [112], atherosclerosis [113], tumor burden [114], dermatitis [115], *Candida albicans* [116], and herpes simplex virus infections [117] as well as in pain [118]. In humans, RvE1 has been identified in the plasma of healthy individuals [119], plasma and synovial fluid from arthritic patients [46], plasma of type II diabetes mellitus patients [54], plasma of peripheral artery disease patients [120], cord blood [55], breast milk [121], and blisters induced by UV-killed *E. coli* [122]. Recently, RvE1 was found by Barden and colleagues to be increased in human neutrophils from subjects with metabolic syndrome following weight loss upon stimulation *ex vivo* [45]. The RvE1 analog mimetic (Fig. 5) evokes anti-inflammatory actions by reducing both neutrophil infiltration and pro-inflammatory cytokine/chemokine production *in vivo* [82]. These findings demonstrate tissue/organ- and cell type-specific actions of RvE1 in the control of a wide range of diseases where excessive inflammation is an underlying pathobiology driven by excessive PMN infiltration and resulting collateral tissue damage.

In the E-series bioactive metabolome, RvE2 stops chemoattractant-stimulated PMN recruitment *in vivo* in murine peritonitis [78] and decreases depression-like behavior in mice [123]. RvE2 has also been identified in the plasma of healthy individuals [119], plasma and synovial fluid of arthritis patients correlating with pain reduction in these

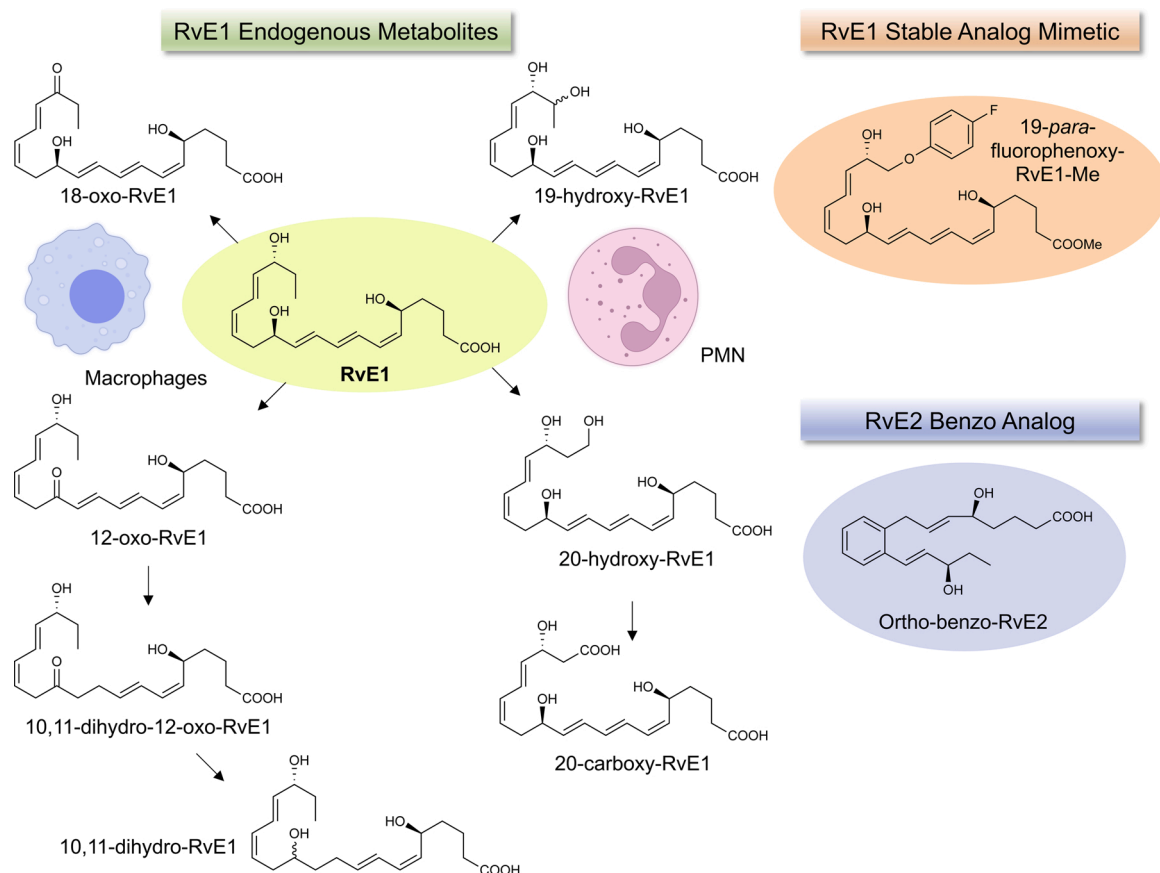


Fig. 5. Further Local Metabolism of Resolvin E1 and Structures: metabolic inactivation. RvE1 is converted to less active metabolites by neutrophils and macrophages [214]. The Resolvin E1 further metabolome is cell-type specific, macrophages carry out dehydrogenation, and neutrophil p450 converts RvE1 to 20-carboxy-metabolites [214]. We prepared and designed stable analogs of Rv [60,82] that delay their rapid local inactivation. For examples, benzo RvD1 analog has been prepared [60] that retains potent bioactions of RvD1, and the 19-p-fluorophenoxy-RvE1 analog delays rapid leukocyte inactivation and is a potent anti-inflammatory and proresolving molecule [82]. Also, the benzo-Resolvin E2 has femtomolar potencies in mouse peritonitis [124].

patients [46], plasma of type II diabetes mellitus patients [54], plasma of peripheral artery disease patients, breast milk [121], and in human blisters induced by UV-killed *E. coli* [122]. Of interest, a novel RvE2 analog, benzo-resolvin E2, was found to display exceptional potency (in the femtomole range) at reducing inflammation *in vivo* [124] (Table 2).

RvE3 decreases allergic airway inflammation via the IL-23/IL-17A pathway [125], reduces depression-like behavior in mice [126], and lowers the incidence of preterm birth in lipopolysaccharide-exposed pregnant mice [127]. Also, RvE3 was identified in both plasma and synovial fluid of arthritic patients [46], plasma of type II diabetes mellitus patients [54], cord blood [55], breast milk [121], and *E. coli*-stimulated human skin blisters [122] (Table 2). Considering the E series metabolome, the precursor of several E-series resolvins, namely 18-HEPE (Figs. 2–4), is also bioactive, inhibiting macrophage-mediated pro-inflammatory activation of cardiac fibroblasts as well as preventing overload-induced maladaptive cardiac remodeling *in vivo*, demonstrating potent actions in cardiac tissue [84]. Considering the structure-activity relationships for the E series resolvins, the 18-deoxy-resolvin E3 (18-deoxy-RvE3) shows potent bioactivity in stopping neutrophil infiltration in mice as well as resolves peritonitis [128]. Recent results indicate that RvE3 is reduced in COVID-19 patients with severe disease compared to moderate disease [24] (Table 1), which highlight the potential significance of SPMs in human disease. E-series resolvins are also found to be endogenous anti-depressants in mouse models [129]. Together these new findings from many independent investigators emphasize the potent structure-based function and bioactions of the E-series resolvins (Table 2).

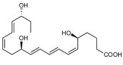
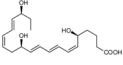
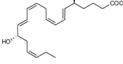
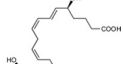
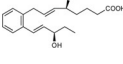
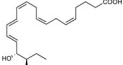
The EPA resolution bioactive metabolome to the E-series bioactive

resolvins produces several potent mediators in this biosynthesis pathway (Table 2 and Fig. 3) that target diverse cell types relevant to inflammation, resolution, depression, and resolution of vascular inflammation. This EPA precursor metabolome may contribute to the clinical impact of omega-3 supplementation as in recent results from cardiovascular disease patients [130] and in human randomized trials, where omega-3 lowered systemic levels of potent pro-inflammatory cytokines associated with inflammaging [131]. It is now clearly demonstrated in humans that omega-3 supplementation is required to increase RvE1, as reported in both serum and plasma of healthy individuals, RvE3 in plasma of patients with peripheral artery disease [120], and circulating RvE1, RvE2, and RvE3 [132]. Welty et al. [133] found that the ratio of the sum of 18-HEPE plus RvE1 to the amounts of leukotriene B₄ is useful in assessing the regression of coronary artery plaques in humans. Keeley et al. [134] recently reported identification of SPMs in women with coronary microvascular dysfunction.

4. D-series resolvins: biosynthesis and stereochemistry

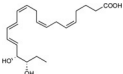
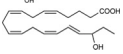
The DHA-derived resolvins and protectins were first uncovered in resolving inflammatory exudates [8,14] and named given their potent actions. The D-series resolvins are biosynthesized via two separate pathways to yield the 17R series [8] and 17S-series resolvins that can involve transcellular biosynthesis with hypoxic vascular endothelial cells and human PMN. There are six potent bioactive members in each, named RvD1, RvD2, RvD3, RvD4, RvD5 and RvD6 [8]. The 17R resolvins are produced from DHA conversion to 17R-hydroperoxy intermediate via acetylated COX-2 and 17S-series resolvins from DHA

Table 2
Inflammation-Resolution EPA Bioactive Functional Metabolome and Related Analogs and Structures.

Name and Abbreviation	Stereochemical name	Structure	Pro-resolving cellular functions and <i>in vivo</i> actions	Organ protection	Locations/origins in humans and animal models
			Limits PMN [21,77,78,80,99] and reduces dendritic cell further tissue infiltration [72,100].	Peritonitis [21,72,77,78,80], air pouch [21], CLP/sepsis [106], bacterial [101], I/R injury [107], diabetes [108], obesity [112], colitis [99,109,110]; lung inflammation [111], kidney injury [199], depression, Alzheimer's [200], atherosclerosis [113,201], bone [81], reduces tumor growth [114], Dermatitis [115], <i>Candida albicans</i> [116], pain [118], and reduces herpes [117]. Nano-delivery of RvE1 repairs gastrointestinal injury and activates wound healing [110,202]	Plasma [119]
Resolvin E1 (RvE1)	5 <i>S</i> ,12 <i>R</i> ,18 <i>R</i> -trihydroxy-6 <i>Z</i> ,8 <i>E</i> ,10 <i>E</i> ,14 <i>Z</i> ,16 <i>E</i> -eicosapentaenoic acid		Reduces pro-inflammatory cytokines [101]. Enhances MΦ phagocytosis & efferocytosis [77,80]. Enhances bacterial clearance [101]. Inhibit pain TRP channels [102]. Regeneration of stem cells isolated from periodontal ligaments [103].		Plasma from arthritis patients [46]
18 <i>S</i> -Resolvin E1 (18 <i>S</i> -RvE1)	5 <i>S</i> ,12 <i>R</i> ,18 <i>S</i> -trihydroxy-6 <i>Z</i> ,8 <i>E</i> ,10 <i>E</i> ,14 <i>Z</i> ,16 <i>E</i> -eicosapentaenoic acid		Stops PMN migration, reduces pro-inflammatory cytokines, and enhances MΦ phagocytosis & efferocytosis [77].	Mouse Peritonitis [77].	Arthritic synovial fluid exudates [46] Plasma of Type 2 diabetes mellitus [54] Plasma of peripheral artery disease (OMEGA-PAD II trial) 0.32–0.62 pg/mL [120]
Resolvin E4 (RvE4)	5 <i>S</i> ,15 <i>S</i> -dihydroxy-6 <i>E</i> ,8 <i>Z</i> ,11 <i>Z</i> ,13 <i>E</i> ,17 <i>Z</i> -eicosapentaenoic acid		RvE4 stimulates macrophage efferocytosis and phagocytosis [61,85]. Stops PMN migration [77,78].	Mouse Hemorrhagic Exudate [85]	Cord blood [55] Human breast milk [121] Blister [122] Metabolic syndrome (weight loss) PMN [45]
Resolvin E2 (RvE2)	5 <i>S</i> ,18 <i>R</i> -dihydroxy-6 <i>E</i> ,8 <i>Z</i> ,11 <i>Z</i> ,14 <i>Z</i> ,16 <i>E</i> -eicosapentaenoic acid		Down-regulates leukocyte integrins [110].	Resolves Peritonitis [77,78], and reduces depression [123].	Plasma 2.3–2.7 pg/mL [119] Plasma of arthritis 68.8 pg/mL [46] Arthritis synovial fluid 774.2 pg/mL [46] Plasma of Type 2 diabetes mellitus [54] Cord blood [55] Plasma of peripheral artery disease (OMEGA-PAD II trial) [120] Human breast milk [121] Human skin blisters [122]
Ortho-Benzo-Resolvin E2 (o-BZ-RvE2)	(<i>S</i> , <i>E</i>)-5-hydroxy-8-(2-((<i>R</i> , <i>E</i>)-3-hydroxypent-1-en-1-yl)phenyl) oct-6-enoic acid		Reduces PMN infiltration <i>in vivo</i> [124]. Inhibits leukocyte migration [83]. Reduces IL-23 and IL-17 [125].	Resolves mouse Peritonitis [124].	
18 <i>R</i> -Resolvin E3 (18 <i>R</i> -RvE3)	17 <i>R</i> ,18 <i>R</i> -dihydroxy-5 <i>Z</i> ,8 <i>Z</i> ,11 <i>Z</i> ,13 <i>E</i> ,15 <i>E</i> -eicosapentaenoic acid		BLT1R antagonist [125].	Peritonitis [83], Mouse lung inflammation [125], reduces murine depression behavior [126], premature birth [127].	Plasma of arthritis [46] Arthritis synovial fluid [46] Plasma of Type 2 diabetes mellitus [54] Plasma of peripheral artery disease (OMEGA-PAD II trial) [120] Cord blood [55] Human breast milk [121] Human skin blisters [122]

(continued on next page)

Table 2 (continued)

Name and Abbreviation	Stereochemical name	Structure	Pro-resolving cellular functions and <i>in vivo</i> actions	Organ protection	Locations/origins in humans and animal models
18S-Resolvin E3 (18S-RvE3)	17R,18S-dihydroxy-5Z,8Z,11Z,13E,15E-eicosapentaenoic acid		Inhibits PMN migration [83,203].	Reduces mouse peritonitis [83, 203].	Metabolic syndrome (weight loss) PMN [45]
18-hydroxy-eicosapenta-enoic acid (18-HEPE)	18S/R-hydroxy-5Z,8Z,11Z,14Z,16E-eicosapentaenoic acid		Reduces pro-inflammatory cytokines [84].	Prevents overload-induced maladaptive cardiac remodeling [84] and metastasis [204].	

conversion via 15-lipoxygenase reaction [8,14]. Each of the D series Resolvins and other SPMs are produced by specific agonist and cell types (Table 3) in well-defined *in vitro* conditions. Resolvin D1 and Resolvin D2 are produced from a transient 7(8)-epoxide intermediate produced via the 5-LOX. Their structures were determined using both GC-MS and LC-MS-MS together with bioassays. The complete stereochemistry of RvD1 and 17R-RvD1 was systematically determined with total organic synthesis and results from rigorous matching studies [135]. The complete structure of Resolvin D2 was also established using this approach and proved to be a potent proresolving molecule [136].

Resolvin D3 and Resolvin D4 are produced [8,14] later in the time course of the acute inflammatory response, appearing in inflammatory exudates after both resolvin D1 and D2 [137]. The complete stereochemical assignment of RvD3's structure was established and its potent bioactions confirmed by total organic synthesis confirmed in two separate series of experiments as 4S,11R,17S-trihydroxydocosa-5Z,7E,9E,13Z,15E,19Z-hexaenoic acid [137–139]. The second synthesis undertaken afforded larger-scale production of RvD3 [138]. The complete stereochemistry of Resolvin D4 was also established using matching studies with materials prepared from total organic synthesis [140,141].

RvD4's complete structure is 4S,5R,17S-trihydroxydocosa-6E,8E,10Z,13Z,15E,19Z-hexaenoic acid. Both RvD3 and RvD4 proved to be potent immunoresolvents stopping further neutrophil infiltration and transmigration, enhancing macrophage phagocytosis and efferocytosis, and reducing cytokines and chemokines, promoting bacterial clearance *in vivo* in mice. Resolvin D3 and Resolvin D4 are produced in resolving inflammatory exudate from the same 4(5)-epoxy-resolvin intermediate as proposed in Ref. [8]. The 4S,5S-epoxy-resolvin intermediate was recently prepared by total organic synthesis and is selectively converted to Resolvin D3 by human neutrophils and to Resolvin D4 by human neutrophils and M2 macrophages [142] by specific enzymes in these phagocytes. RvD4 reduced thrombus in pathologic thrombosis [143–145]. Morita et al. [146] also reported a stereocontrolled synthesis of resolvin D4.

Morbidly obese human subjects have higher amounts of RvD4 and other SPMs that are reduced post-surgery in diabetes, suggesting ongoing inflammation in these patients [42]. Resolvin D5 plays a critical role in host defense, enhancing bacterial killing and clearance [11,147]. The structure of resolvin D5 was established and confirmed with results from total organic synthesis [148,149], leukocyte biosynthesis, and from enzymatic studies [150] with 15-lipoxygenase-2. RvD5 is increased in human blood with n-3 supplementation [38] and is present in human skin in lesions of psoriasis [151]. With skin cells, RvD5 reduces expression of IL-24 and S100A12 with human keratinocytes [151] and remains elevated one year after discharge in ICU patients with abdominal septic shock [152], suggesting the need for long-term follow-up of ICU patients. Resolvin D5 and other D-series resolvins reduce both inflammatory pain and neuropathic pain, showing sex-dependent dimorphism in mice [153]. In addition to the innate system, SPMs are also biosynthesized [154] and function in the adaptive immune system

regulating T-cell responses [155] and B cell antibody production [156] that is relevant in infections such as COVID-19. Recently, RvD5 was found to also act on T cells to reduce experimental arthritis [157].

Resolvin D6 was first uncovered in resolving inflammatory exudates along with the other D-series resolvins and protectins biosynthesized from DHA [8]. These novel and unique structures were determined using both LC-MS-MS and GC-MS fragmentation and bioassays. Resolvin D6 has a role in reducing muscle inflammation associated with injury and aging [48] and in tendon overuse [49]. Recently, a Resolvin D6 isomer and Elovanoic-N32 were discovered to reduce ACE2 and binding of the virus spike protein to human corneal epithelial cells of the eye following injury or exposure to IFN γ [158,159] and to stimulate nerve regeneration, wound healing and pain [160]. Human periodontal stem cells also produce Resolvin D6 and other SPM [161]. The complete structure of the Resolvin D6 novel isomer responsible for reducing neuropathic pain and nerve regeneration was recently elucidated and found to be RR-RvD6 prepared by total organic synthesis [162].

DHA is enriched in neural tissues, nerves, and brain. SPMs are bioactive products via enzymatic pathways that are highly conserved in evolution from fish to humans [163]. Trout brain produces Resolvin D5, RvD1 and RvD2 as well as neuroprotectin D1, indicating that these chemical signals are conserved structures from fish to humans [164]. Atlantic salmon also produce resolvins *de novo*, which are reduced in amounts with baking [165]. DPA of the n-3 pathways is also a precursor to SPMs [56]. The consequence of consuming fish that contain resolvins and/or other SPM as well as prostaglandins remains to be determined.

5. The Protectin and Maresin families of potent bioactive mediators: biosynthesis and stereochemistry

Within the inflammatory exudates (Fig. 1) as neutrophils enter the exudates [8], DHA is converted to conjugated triene structures, e.g. 10,17-diHDHA, that include neuroprotectin D1, which protects retinal pigmented epithelial cells of the eye [166] and stops PMN infiltration to the brain, protecting neural tissues from leukocyte-mediated collateral tissue damage and inflammation [167], and stimulates wound healing of corneal epithelial cells [168]. Both 17S-resolvins and protectins are produced from the 17S-HpDHA intermediate that is the biosynthetic product of human 15-LOX (12/15-lipoxygenase of the mouse) with DHA [14] and subsequent enzymatic steps to produce each of the potent bioactive molecules. The name *protectins* was coined from the potent organ-protective actions and anti-inflammatory—pro-resolving actions of this family of mediators. The prefix *neuro* in neuroprotectin D1 (NPD1) reports the tissue of origin of these bioactive molecules [166], which are also produced by exudate leukocytes of the innate immune system [8,14]. NPD1 reduced stroke damage [167], protects lung tissue [169] and kidneys from injury [170], and increases neural cell survival [171]. Macrophages, T cells and neutrophils produce protectins from DHA. The complete stereochemistries of the bioactive neuroprotectin D1/protectin D1 and its natural biosynthesis isomers produced on

Table 3
Agonist and Cell Types Producing SPM *in vitro*.

Agonist	Cell Type	Incubation	SPM	Reference
ASA (500 µg/air pouch)	TNF-α induced exudate (6 h)	2.3 × 10 ⁶ leukocytes/ pouch FVB mice	18R HEPE	[21]
EPA (500 µg/ air pouch)	Air pouch leukocyte		Resolvin E1	
IL-1β-treated Human HUVEC	HUVEC	IL-1β (24 h) and ASA	18R HEPE	[21]
Serum-treated zymosan 100 ng/ mL	Human PMN	PMN 30 × 10 ⁶ , 30 min	Resolvin E1	[21]
ASA recombinant COX-2 EPA products		STZ (100 ng/mL)	Lipoxin A ₅	
		PMN 30 × 10 ⁶	Lipoxin A ₄	
FMLP 10 ⁻⁷ M	GM-CSF Human PMN	200 pM rhGMCSF	Lipoxin B ₄	[205]
		90 minutes		
A23187 (20 min)	Trout Macrophages	10 × 10 ⁶ cells, A23187	Lipoxin A ₄	[206]
		20 min, 18 °C	Lipoxin A ₅	
TNF-α (50 ng/mL) 24 h	Human Microglia	ASA, 30 min	17R-HDHA	[8]
Hypoxia	HUVEC	ASA, TNF-α, IL-1β + Hypoxia	17R-HDHA	[8]
		DHA (20 µg/ 1 × 10 ⁶)		
ASA	Inflammatory exudates	6 h, FVB mice	17R-Resolvin D5	[8]
	Mouse ASA		17R-Resolvin D3	
Zymosan	Human PMN	PMN (50 × 10 ⁶ cells/ ml)	D series Resolvins	[8]
		Zymosan 100 ng/mL		
		17R HDHA (5µg/mL)		
IL-1β or A23187	Retinal ARPE-19 cells	IL-1β (6 h)	NPD1	[166]
		10 × 10 ⁶ cells +	Resolvin D5	
TLR-7 Agonist (R-848)	Human monocytes	R-848 (100 µM)	Protectin D1	[207]
		1 h, 37 °C		
	Apoptotic PMN	10 × 10 ⁶ cells	E series Resolvins	[17]
			D series Resolvins	
Mouse apoptotic PMN	M0 Macrophages	Time course 120 min efferocytosis	Lipoxin A ₄ , Resolvin E1	[80]
			Protectin D1	
ASA + EPA	Human M0 Macrophages	EPA (20µM) for 45 min	Resolvin E1	[80]
<i>E. coli</i>	M2 human Macrophages	5 × 10 ⁶ M2 Macrophages	Resolvin D5	[18]
		90 min, 37 °C		
sPLA ₂ Type V	Microparticle	Zymosan peritonitis (1 mg) exudates 48 h	17-HDHA	[191]
			14-HDHA	
<i>E. coli</i> (10 ⁵ CFU)	Infectious Leukocytes Exudate	In vivo collected exudate 24 h	Resolvin D3	[138]
18-HEPE (5µg)	Human PMN	Hypoxia PMN plus	Resolvin E1	[78]
		Zymosan (100 µg/mL)	Resolvin E2	
		LPS (1µg/mL) 20 min	Lipoxin A ₄	
LPS/ FMLP	GM-CSF Human Macrophages	+ FMLP (1µM) 10 min	17-HDHA	[208]
		37 °C		
Zymosan peritonitis (1 mg)	Eosinophils	In vivo collected exudate 24 h	Lipoxin A ₄	[209]
			Protectin D1	
HMGB1+ C1q	Human Monocytes	HMGB1 (1µg/mL)	Lipoxin A ₄	[20]
		C1q (25 µg/mL)	Resolvin D1	
		6 h	Resolvin D2	
HMGB1 alone	Human Monocytes	HMGB1 (1µg/mL)	Leukotriene B ₄	[20]
	Mouse Peritoneal Exudates		Resolvin E2	
Carbon monoxide (CO) + zymosan <i>in vivo</i> in mice	0.1 mg/ zymosan	250 ppm CO	Resolvin D1	[210]
			Resolvin D2	
			Maresin 1	
Zymosan peritonitis (1 mg)	Human MCSF Macrophages	Endogenous Maresin 1	Maresin 1	[15,175]
		Stereochemistry		
Physiologic Hypoxia (1 % oxygen)	Human M2 Macrophages	24 h hypoxia chamber	RvE4	[85]
			D-Series Resolvins	
EPA (1 g)	Human plasma collected (3 h)		18-HEPE	[77]

enzymatic processing of DHA were established using materials prepared by total organic synthesis and qualified with NMR [172]. NPD1/PD1 activates endogenous resolution programs, shortening the time to resolve [80].

The 17-epi-protectins such as 17R-PD1/NPD1 are biosynthesized *via* aspirin-acetylated COX-2 enzyme, as for example in hypoxic vascular endothelial cells [173], which proved to be potent protective and pro-resolving molecules [reviewed in Ref. 174]. The complete stereochemistry of the 17-epi-NPD1/PD1, also known as the aspirin-triggered (AT)-NPD1/PD1, was assigned using materials prepared by total organic synthesis. The endogenous AT- or R epimer of NPD1/PD1 proved to be 10R,17R-dihydroxy-docosa-4Z,7Z,10E,12E,14Z,19Z-hexaenoic acid with potent proresolving actions [reviewed in Ref. 174, cf. and see references within]. Other stereo and geometric isomers of NPD1/PD1 do not possess these potent anti-inflammatory—pro-resolving actions.

These properties of NPD1/PD1 may be useful in the design of novel therapeutic agents for neurodegenerative diseases where neural inflammation plays a central role in disease pathology.

Later in the progression of the acute inflammatory response (Fig. 1), when macrophages appear and enter the exudates with directives for wound healing and homeostasis, these cells convert DHA to the maresins (*macrophage mediators in resolving inflammation*), which are proresolving and stimulate tissue regeneration [15,175]. The complete stereochemistry of Maresin 1 (MaR1) is 7R,14S,dihydroxydocosa-4Z,8E,10E,12Z,16Z,19Z-hexaenoic acid and was determined by matching the endogenous MaR1 produced by macrophages to compounds prepared by total organic synthesis. MaR1's proresolving actions are complemented by this molecule's ability to stimulate tissue regeneration and reduce pain. MaR1 inhibits capsaicin-induced TRPV1 currents in neurons [175]. MaR1 is biosynthesized *via* an epoxide intermediate enzymatically

produced from the DHA-derived lipoxygenase product 14-HpDHA [15] as determined by acid methanol trapping studies and analyses of the resulting products. The role of this unique 13S,14S-epoxy-maresin was confirmed by total organic synthesis and its conversion to MaR1 [176, 177] by M2 macrophages, where this epoxide also proved to be bioactive, stimulating the phenotype switch from M1 to M2 macrophages.

6. Cys-SPM

The enzymatic conversion of lipoxygenase produces hydro(peroxy)-containing intermediates that are transient and rapidly transformed to epoxide-containing intermediates that play critical roles in the stereochemical specific biosynthesis of Resolvins, Protectins and Maresins in each pathway [for review, see Ref. 174]. Evidence for the cellular production of unstable epoxide intermediates within each SPM biosynthesis pathway was obtained using acid-methanol trapping [8,14,15,135,154]. Confirmation of the role of these transient epoxide-containing intermediates was obtained from studies with leukocytes, isolated enzymes, and their stereoselective total organic synthesis. The 13S, 14S-epoxy-maresin was prepared with Professor Nicos Petasis and his team [176], and the 16,17-epoxy-protectin was prepared with Professor Trond Hansen, Jørn Tungen and Marius Aursnes [178]. Recently, the 4S, 5S-epoxy-resolvin was synthesized by total organic synthesis, and its enzymatic conversion to Resolvin D3 and Resolvin D4 proved to be cell type specific with human phagocytes [142]. Each epoxide intermediate is also pivotal in the enzymatic biosynthesis of the cys-SPM, e.g. MCTRs [179], which stimulate tissue regeneration and are proresolving, PCTRs [178] and RCTRs, each with 3 members in their biosynthetic pathways; their complete stereochemistry has been determined and confirmed their potent bioactivities [180] with both Dr. Bernd Spur and Dr. Nicos Petasis [181,182]. With these epoxides in hand, we've focused on the enzymes responsible for their conversion to potent cys-SPMs [142,183], as well as specific SPMs.

Essential fatty acids, *i.e.*, EPA and DHA, can undergo autooxidation reactions that are widely known to lead to products that are pro-inflammatory; however, these non-enzymatic reaction products are not stereoselective for the most part in their production and give rise to racemic mixtures of products that do not share the properties or potent biologic functions of the SPMs reviewed herein. The stereoselective biosynthesis of the resolvins within human leukocytes leads to their stereochemically defined structures for the SPMs that activate specific cell surface GPC receptors with nanomolar binding constants [reviewed recently in Ref. 184]. The biosynthesis of SPM in humans requires substrate EPA and DHA in adequate amounts and locations *in vivo* to enable SPM biosynthesis *in vivo* in humans; for examples, see [38–40,50, 185–187], to yield precise chemical structures of the SPMs with protective function for the host [188]. These early results of our studies underscore the importance of precision nutrition in the optimal progression of host defense and resolution of the acute inflammatory response in humans and model organisms [189].

7. In summation

The results reviewed here provide evidence that synthetic stereochemically defined potent bioactive SPMs matching the endogenous molecules produced by human cell types, *e.g.*, neutrophils, lymphocytes, and macrophages (Fig. 1B), are now in wide use worldwide in experimental disease studies and as standards for targeted LC-MS/MS-based profiling and lipidomics/metabolomic human studies from many independent investigators worldwide confirming that SPMs are produced *in vivo* in humans. Omega-3 supplementation is required and increases SPM production *in vivo* [50]. Each member of the E-series resolvins, *i.e.*, RvE1, RvE2, RvE3 and RvE4, are now documented in human tissues in several independent investigations that confirm their original structural elucidation. The physiologic function(s) of the E series resolvin metabolomes in humans are still evolving. The current results available from

human studies indicate that the SPMs are indeed produced in humans when suitable substrates are available *in vivo*.

The potent functions of each of the stereochemically defined SPMs in resolving and reducing the magnitude of inflammation *in vivo* are now demonstrated by many independent investigations around the world with diverse experimental animal models of disease: >1420 publications were reported for resolvins in PubMed.gov as of Dec. 2021 (with resolvins as search term) that confirm the potent pro-resolving properties of each of the SPMs and their novel structures as originally described, triggered *via* local hypoxia in the resolving inflammatory milieu [8,14,15]. Given the current pandemic and the identification of resolvins as well as the other SPMs in human COVID-19 (Table 1), the availability of SPM and several of their deuterium-containing labels for use as standards and rigorous determinations and authentication methods enable targeted LC-MS-MS-based profiling that the Serhan lab initially introduced [27–29]. These can be tested in long-COVID patients to assess SPM, their *de novo* production and potential local cellular and organ functions with precision nutrition interventions that can now be rigorously tested as, *e.g.* to consider whether they can reduce the symptoms of long COVID and acute COVID-19 infections. The SPMs have proven to be potent proresolving molecules in resolving inflammation and pain in experimental animals and with isolated single cell analysts with human leukocytes. Given that SPMs are conserved structures in evolution as discussed herein, it is very possible that increasing SPM production *in vivo* can permit them to function in humans to reduce pain, resolve tissue inflammation and clear microbes as well as activate regeneration of damaged tissues.

Clinical studies along these lines with interventions for precision nutrition [190] are now made possible with the stereochemically defined SPMs and targeted LC-MS-MS-based metabololipidomic profiling [27,28] as required tools for this endeavor. In a clinical trial where a proresolving mimetic LX/Rv stable analog was employed topically on inflamed gingival tissue, subjects had reduced gingival inflammation as well as increased production of SPMs in their peripheral blood samples [63]. These human results suggest that SPM therapies can increase endogenous SPM and resolution in a positive feed-forward mechanism as uncovered earlier in experimental animals, where we found that SPMs each activate endogenous resolution programs to shorten recovery times from inflammatory challenge [80]. Local delivery of pro-resolving molecules with nano-pro-resolving medicines such as the resolvins and lipoxins delivered in humanized nano particles has advantages as well in resolving inflammation and activating wound healing and repair [191]. This concept for the local delivery of resolvins has now been studied in a wide range of engineered materials to successfully activate endogenous resolution programs *in vivo* [192,193]. Hence, rigorous determinations of whether the state of resolution of inflammation can be achieved in humans with precision nutrition is of vital importance given the impact of the COVID-19 variants and long COVID on human health, the ongoing pandemic, and the unmet need in public health. Have the stereochemistry studies of the SPM and their human biosynthesis pathway(s)-metabolomes each from omega-3 precursors prepared us for this paramount challenge? Are we ready?

Can precision nutrition targeted to increase SPMs *in vivo* enable human subjects to return to homeostasis more rapidly (recover more swiftly) following the initial insult of the COVID viral infection? It can also be considered whether there are functional roles for SPMs in peripheral blood circulation. Are they functional in the local milieu, where they can directly regulate leukocyte response in whole human blood [75,194], or in transit and/or leaking into peripheral blood from other sites/organs within the body, possibly from sites of infectious inflammation in multiple organs? Our field is prepared to address these challenges and is armed with the required tools and ample experimental evidence now available from investigators around the world's scientific community interested in resolving inflammation and infection (cited herein). Only time, resources and rigorous testing-documentation will give us the much-needed answers on precision nutrition and its potential

in human public health and the potential for SPMs in resolution physiology-pharmacology.

Author contributions

C.N.S., S.L. and R.N. composed and contributed to the preparation of this manuscript, tables, and figures.

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