Unresolved inflammation is associated with several widely recurrent aging-associated diseases such as arthritis, periodontitis, metabolic disorders, atherosclerosis, and neurodegeneration. Endogenous mechanisms that curtail excessive inflammation and prompt its timely resolution are of considerable interest. In recent years, previously unrecognized chemical mediators derived from polyunsaturated fatty acids were identified as endogenous specialized pro-resolving lipid mediators (SPM) that control both the magnitude and duration of acute inflammation and activate resolution. Lipoxins (LX), resolvins (Rv), protectins (PD), and maresins (Mar) are possess distinct chemical structures, bind to specific G-protein coupled receptors (GPCRs) in a stereospecific manner, and regulate biological pathways to promote resolution in several pre-clinical experimental settings of age-related inflammatory diseases. This review highlights the biosynthesis of SPM and cellular mechanisms that underscore their beneficial bioactions in the regulation of acute inflammation in age-related diseases.

The elucidation of these mechanisms operating in vivo to keep acute inflammation under physiologic boundaries and stimulate resolution opened many new opportunities in resolution pharmacology to target aging-associated chronic inflammatory pathologies.
Resolution of Inflammation: An Active Process Regulated by Specific Chemical Mediators

Resolution has been well described by pathologists more than 100 years ago as the time when the number of neutrophils infiltrating the inflamed tissue is decreasing [1]. This process has been traditionally considered passive, simply due to the attenuation/dissipation of pro-inflammatory signals. Pioneer work from dr. Serhan et al. [9-12] and from many others worldwide [4,13-16] have demonstrated that resolution of inflammation is instead an active process orchestrated by specific chemical mediators that turn on biochemical pathways and MФ functions to enable the return to homeostasis. Among them, endogenous lipid mediators (LM) biosynthesized from essential Polyunsaturated Fatty Acids (PUFA) play essential roles in resolution acting as “resolution agonists” to a) keep inflammation under physiological boundaries preventing excessive PMN infiltration and b) expedite the complete return to homeostasis stimulating effectorcysis of MФ (Figure 1). Therefore, they represent a new genus of specialized pro-resolving lipid mediators (SPM) [17,18] or immunoresolvents since they act by finely regulating immune processes to promote resolution and the return to homeostasis [19-21]. The SPM genus include lipoxins (LX), resolvins (Rv), protectins (PD), and maresins (Mar) that are enzymatically biosynthesized by lipoxigenase (LO)-driven pathways from Arachidonic Acid (AA), Eicosapentaenoic Acid (EPA), or Docosahexaenoic Acid (DHA) that rapidly appear in exudates and are made available for the conversion into immunoresolvent [22] (Figure 2). In human system, both resident and blood cells contribute to the biosynthesis of SPM, which can be detected intact, at pico- to nanogram levels, in biological fluids [23,24] as well as in tissues in basal conditions and in response to stimuli such as physical exercise [25,26], inflammation [27], or vascular damage [28]. In addition to the LO-pathway, a distinct biochemical route for the biosynthesis of SPM is operative in the vasculature of inflammatory loci. This is initiated by aspirin, a derivative of salicilates, upon acetylation of cyclooxygenase- (COX) 2. The covalent modification of COX-2 shifts the enzyme activity from endoperoxidase into a LO-like, initiating the biosynthesis of epimeric forms of SPM, such as 15R-epi-LXA4, coined “Aspirin Triggered Lipoxin” (ATL) [29]. Notably, ATL, produced in vivo in human subjects taking aspirin [30], proved to be responsible for the local anti-inflammatory actions of low-dose aspirin [30]. Hence, in addition to block formation, aspirin impinges on resolution by triggering the biosynthesis SPM (Figure 2) [31].

In order to define resolution in unbiased, quantitative terms, mathematical resolution indices were introduced by Bannenberg et al. determining the cellular changes in exudates following an acute inflammatory stimulus (namely zymosan A particles from S. cerevisiae, a Toll-like receptor activator). Resolution indices encompass: T\textsubscript{max} i.e., time point of maximum PMN infiltration ($\Psi_{\text{max}}$); T\textsubscript{50}, time necessary to achieve 50% reduction in PMN number ($\Psi_{50}$) from $\Psi_{\text{max}}$; resolution interval (R = T\textsubscript{50} - T\textsubscript{max}); time interval between T\textsubscript{max} and T\textsubscript{50} [32]. The introduction of resolution indices permits the evaluation of pro-resolution bioactions of endogenous chemical mediators or pharmacological agents in pre-clinical models of inflammatory diseases [33-35].

Other chemical mediators are involved in endogenous resolution pathways to switch off leukocyte infiltration and restore homeostasis. Among them are proteins such as the glucocorticoid-induced annexin (Anx) A1 and galectins, which tune the inflammatory response and bring about homeostasis (for recent reviews see refs [36,37]. Furthermore, recent results demonstrate that small inhibitors of cyclin-dependent kinases [3,38] and histone deacetylases [39] can promote resolution by inducing PMN apoptosis and stimulating their prompt removal by MФs, indicating that resolution can be pharmacologically targeted. The appreciation of resolution as a programmed process governed by specific chemical mediators offers opportunities in the uncharted...
terrain of resolution pharmacology, namely harnessing endogenous controllers of inflammation as therapeutics or biotemplates for new drugs to treat inflammation-related diseases [18,40]. For example, AnxA1 served as model for the generation of peptides [41,42] and engineered nanoparticles [43] that dampen inflammation and protect from tissue damage. Likewise, several LX stable analogs obtained by organic synthesis proved to have anti-inflammatory and organ protective activities [44-46] and results by Norling et al. demonstrate the efficacy of human neutrophil-derived nanoparticles carrying a benzo-LX analog in reducing peritoneal and joint inflammation [47]. Moreover, RX-10045, a synthetic resolvin analog formulated by Resolvyx Pharmaceuticals Inc. for topical application, proved safe and effective in reducing the severity of dry eye syndrome in a phase II placebo controlled clinical trial (see http://clinicaltrials.gov. Entry Identifier: NCT00799552) and have moved forward to phase III clinical trial with Celtic Therapeutics. Finally, a recent placebo-controlled, randomized, comparative study demonstrated that a LX analog significantly ameliorates clinical parameters of juvenile eczema [48], further translating results from pre-clinical models to humans and establishing the effectiveness of SPM-based pro-resolution pharmacology.

Importantly, resolution is not synonymous of anti-inflammation. This is because, in order to be considered a “pro-resolver” a chemical entity, in addition to serve as “stop signals” for leukocyte trafficking and other cardinal signs of inflammation (e.g. swelling, pain), must stimulate efferocytosis by MФ, favor the antibacterial activities, and promote tissue repair. Along these lines, while COX and LO inhibitors reduce some of the cellular events of the inflammatory reaction (e.g. edema formation, PMN recruitment, and pain), they dramatically impairs resolution [33,49]. In contrast, aspirin and glucocorticoids act synergistically with endogenous pro-resolution pathways [13]. Complete resolution also requires the clearance of microparticles (MPs) shed by activated or apoptotic cells in inflammatory loci from plasma membranes. MPs are now recognized as “specialized shuttles” of bioactive molecules with important roles in inflammation and resolution. Indeed, a subset of PMN-derived MPs that exert anti-inflammatory actions was identified [42,46]. Furthermore, Norling et al. developed, from human PMN, novel nano-proresolving medicines (NPRMs) containing SPM that proved bioactive in reducing acute inflammation in vivo, expediting resolution, and promoting wound healing [50]. Additional biological properties of NPRMs have recently been demonstrated in a modified focal microfluidic chamber [51] on isolated human leukocytes, further confirming the possibility to
exploit NPRMs for delivering endogenous pro-resolution mediators therapeutically.

Biosynthesis of SPM from PUFA

The identification SPM was achieved using a self-limited or naturally resolving acute inflammation model in vivo and a systems approach [11,52] and reviewed [17]. For this, the murine dorsal air pouch was ideal because it permitted isolation of inflammatory exudates for cellular analyses, proteomics, [11,52] and direct LM-lipidomics of bioactive products, as well as their inactive precursors and further metabolites, during a self-limited acute inflammation, i.e., the natural means by which inflammation returns to homeostasis. With this systems approach it was possible to establish the local and temporal dissociation of LM biosynthesis [32] from onset to resolution phase of inflammation. Indeed, in this setting, the eicosanoid biosynthesis underwent a "class switch" with the deactivation of the biosynthesis of pro-inflammatory leukotrienes (LT) and the initiation of LX and Rv production [12]. LM lipidomics using liquid chromatography-tandem mass spectrometry (LC-MS/MS) coupled with informatics permit profiling of closely related compounds and identification of new molecules. Retrograde, both biogenic and total organic, synthesis allows the complete elucidation of chemical structure, stereochemistry, and physical properties, along with the recapitulation of the in vivo biosynthetic pathway [19,53,54]. The matching/identification of LM is usually carried out with at least two different instruments and/or solvent systems and the criteria to identify a known LM are the following: a) LC retention time should match by coelution with the LM authentic standard; b) UV chromophore should match the synthetic and authentic LM (i.e., λ_max and band shape); as well as c) > 6 diagnostic ions of tandem MS/MS spectrum. Recently, a new set of SPM derived from DHA has been identified with targeted LM metabolomics [21], providing new mechanisms for the beneficial actions of PUFAs. The next paragraph will illustrate biosynthetic routes and chemical properties of the main SPM.

Lipoxins

LXs are "lipoxygenase interaction products" derived from the enzymatic conversion of arachidonic acid (AA) via trancellular biosynthesis during cell-cell interactions occurring during inflammation [55]. LXA₄ and B₄ were the first SPM identified by Serhan et al. [9,10]. Although LXs were identified in 1980s in the Samuelson laboratory [9], their potent bioactions were uncovered some years later when it became clear that they act as ‘stop signals’ of further PMN infiltration [56] and as potent stimuli for the non-phlogistic recruitment of monocytes [57] and MΦ efferocytosis [58] (recently reviewed in [40]). In humans, sequential oxygenation of AA by 15-LO and 5-LO, followed by enzymatic hydrolysis, leads to the biosynthesis of LXA₄ and B₄ in monocytes [56] and as potent stimuli for the non-phlogistic recruitment of AA to pro-inflammatory and prothrombotic eicosanoids; serving as an alternate substrate for the 5-series LTs that are less potent than 4-series LTs; conversion by COX to 3-series prostanooids that also maintain antiinflammatory actions) [67,68,70] have not been generally accepted due to the lack of molecular evidence in vivo and the high concentrations of ω-3 PUFAs required in vitro to achieve putative "beneficial actions". To address the molecular basis for anti-inflammatory properties of ω-3 fatty acids, an unbiased LC-MS/MS-based informatics approach was developed to identify novel mediators generated from ω-3 precursors during acute inflammation in vivo. Using this approach, EPA was found to be enzymatically converted into novel potent LMs coined resolvins (an acronym of resolution phase interaction products) because a) they are produced during cell-cell interactions occurring in the resolution phase of acute inflammatory response; (b) "stop" further neutrophil entry to sites of inflammation, and (c) reduce exudates [11,32,52,71,72]. EPA-derived E-series Rv are endogenously biosynthesized in vivo in resolving murine exudates and in isolated human cells by isolated cells (e.g, endothelial cells -leukocyte interaction) and in whole blood (vide infra). The complete stereochemistry of first member of this family, RvE1, has been established as 5S,12R,18R-trihydoxy-6Z,8E,10E,14Z,16E-EPA [73]. In vascular endothelial cells, aspirin acetylated COX-2 converts EPA into 18R-Hydro(peroxy)-Eicosapentaenoic acid (HEPE), which is rapidly taken up by activated leukocytes (e.g., PMN) and further metabolized into RvE1 (Figure 2). Interestingly, chiral HPLC analysis indicated that the 18R-HEPE isomer was dominant to its epimer 18S-HEPE in human plasma from healthy volunteers taking EPA, whereas human subjects who were administered aspirin before EPA had more 18S- than 18R-HEPE. These results indicate that aspirin might promote 18S-HEPE production as well as 18R-HEPE from ingested EPA [74]. Notably, 18S-HEPE can also be converted to RvE1 and RvE2 by human recombinant 5-LO and LT A4 hydrolase, a LTB₄-synthesizing enzymes [74], and RvE1 is also produced via cytochrome P450-driven oxygenation of EPA [11] and by Candida albicans [75]. RvE2 (5S, 18-dihydroxy-EPE) is biosynthesized in resolving exudates and in human whole blood via reduction of 5S-hydroxyprostanoids, 18-hydroxy-EPE, an intermediate in the biosynthetic pathway of RvE1 [76-78]. Conversely, novel EPA-derived SPM, namely 18R-RvE3 (17R, 18-dihydroxy-5Z, 8Z, 11Z, 13E, and 15E-EPE) and epimeric 17R, 18S-RvE3, that possess potent anti-inflammatory actions both in vitro and in vivo are biosynthesized via 12/15-LY by ecosinophils [79,80].
D-series resolvins

Earlier LC-MS/MS-based analyses of resolving exudates from mice given DHA and aspirin provided the first evidence for the formation of novel endogenous di-hydroxy-containing mediators [53]. Recapitulation of biosynthetic pathways using isolated cells and recombinant enzymes established potential origins of novel compounds isolated from resolving exudates in vivo. Indeed, hypoxic human endothelial cells COX-2 converted DHA to 13-hydroxy-DHA that switched with ASA to 17R-HDDA that can be transformed to di- and trihydroxy products by human PMN. These compounds were termed “aspirin triggered” D-series resolvins [52]. Remarkably, in the absence of aspirin, D-series resolvins carrying the 17S-hydroxy group were identified in murine exudates and isolated human cells [52,71]. The enzymatic processes leading to the formation of 17S- and 17R-RvD1 are shown in Figure 2. Following the complete organic synthesis, the stereochromy of 17S-, 17R-RvD1, and RvD2 were established as 7S, 8R,17-trihydroxy-4Z,9E,11E,13Z,15E,19Z-docosahexaenoic acid (17R-RvD1), 7S, 8R, 17-trihydroxy-4Z,9E,11E,13Z,15E,19Z-docosahexaenoic acid (17R-RvD1) [53], and 7S, 16R, 17-trihydroxy-4Z, 8E, 10Z, 12E, 14E, 19Z-docosahexaenoic acid (RvD2) [81]. Additional members of this family have identified (RvD3-RvD6). Each of these arises by similar biosynthetic routes, but has distinct chemical structures and potentially additional bioactions that are now being unveiled [20,82].

(NEuro) protectins

In addition to D-series Rvs, DHA also serves as precursor of a new family of LM characterized by a conjugated triene system and two alcohol groups called protectins (PD), in view of their protective actions in neural tissues within the immune system, while the prefix neuroprotectin gives the tissue localization and site of action. The structure of the founding member of this family, PD1, was first disclosed in a report on the isolation and elucidation of resolvins [52,71] and its complete stereochemistry later established as 10R,17S-dihydroxy-docosa-4Z,7Z,11E,13E,15Z,19Z-hexaenoic acid [72]. In addition to PD1, several stereo- and positional isomers that also possess lower bioactivity than PD1 were identified in human and mouse tissues. These include 10S, 17S-dihydrox, 4S,17S-dihydrox, 7S,17S-dihydrox, and 22-hydrox-10,17-docosatriene (a putative inactivation product of PD1) [53,72]. Finally, a novel aspirin triggered COX-2 driven pathway that biosynthesizes the 17R-epimeric form of PD1 from DHA has been reported [83] (Figure 3). The total organic synthesis and complete stereochemical assignment of AT-PD1 (10R,17S-dihydroxy-docosa-4Z,7Z,11E,13E,15Z,19Z-hexaenoic acid) were recently achieved [84].

Maresins

Macrophages have pivotal tasks in restoring homeostasis [2] and are main SPM-synthesizing cells during this active process. For
example, MΦ ingestion of apoptotic PMN concomitantly initiate tissue resolution [15,16] and the biosynthesis of LXA4, RvE1, and PD1, but not LTB4 [33,85]. Along these lines, maresins are a new family of SPM produced by MΦs identified with LM-metabolomics [86]. A 12/15-LO-dependent biochemical pathway converts DHA into 14-hydroxydocosahexaenoic acid (HDHA), which is rapidly converted by isolated MΦ into a new set of products, whose molecular structure was established [54] and recently confirmed [19]. Macrophage 12-LO converts this 14-HDHA intermediate into a 13,14-epoxy precursor of 7,14-dihydroxydocos-4Z,8E,10Z,12E,16Z,19Z-hexaenoic acid, named maresin (from macrophage mediator in resolving inflammation) 1 (MaR1) (Figure 2) [54]. The complete stereochemical assignment and total organic synthesis of Mar1 have been achieved [19] and (MaR1) (Figure 2) [54]. The complete stereochemical assignment and total organic synthesis of Mar1 have been achieved [19] and double bond geometry and chirality of 13,14-epoxy DHA elucidated and total organic synthesis of Mar1 have been achieved [19] and recently confirmed [19]. Macrophage 12-LO converts this 14-HDHA intermediate into a 13,14-epoxy precursor of 7,14-dihydroxydocos-4Z,8E,10Z,12E,16Z,19Z-hexaenoic acid, named maresin (from macrophage mediator in resolving inflammation) 1 (MaR1) (Figure 2) [54]. The complete stereochemical assignment and total organic synthesis of Mar1 have been achieved [19] and recently confirmed [19].

### LXA4 and ATL, analogs

| Target cell         | Actions                                                                 | References                          |
|---------------------|--------------------------------------------------------------------------|-------------------------------------|
| PMN                 | Inhibit chemotaxis, adhesion to/transmigration across endothelial and epithelial cells. Reduce ROS generation, CD11b/CD18 expression, pro-inflammatory cytokines | [117,155-160]                       |
| Monocytes/MΦs       | Stimulate non phlogistic chemotaxis and adhesion. Enhance phagocytic activity | [33,57,58,161,162]                   |
| Eosinophils         | Inhibit chemotaxis, IL-5, and eosinotoxin secretion                      | [122,163,164]                       |
| Platelets           | Inhibit Porphyromonas gingivalis-induced aggregation                     | [159]                               |
| T lymphocytes       | Reduce TNF-α production and increase CCR5 expression                     | [165,166]                           |
| B lymphocytes       | Decreases IgM and IgG production by activated B cells and their proliferation through ALX/FPR2 |                                   |
| NK cells            | Block cytotoxicity. Enhance pro-resolution NK-mediated apoptosis of eosinophils and PMN | [112,166,169]                       |
| Endothelial cells   | Block ROS production, inhibit VEGF-induced proliferation, decrease adhesion molecules. Stimulate prostacyclin and NO production. Enhance HO-1 expression | [31,111,170-174]                   |
| Epithelial cells    | Inhibit IL-8 release. Enhance epithelium repair through K channel activation and tight junction increase | [175-177]                           |
| Vascular smooth muscle cells | Counteract PDGF-induced migration. Regulate cell phenotype | [178]                               |
| Fibroblasts         | Inhibit proliferation, pro-inflammatory cytokines, and MMP-3             | [179,180]                           |
| Mesangial cells     | Inhibit proliferation and pro-inflammatory cytokines                     | [181-183]                           |

### LXB4 and analogs

| Target cell | Actions                                                                 | References |
|-------------|--------------------------------------------------------------------------|------------|
| Monocytes   | Stimulate non phlogistic recruitment and adhesion                        | [161,164]  |
| PMN         | Inhibit migration and adhesion                                           | [157,164]  |
| NK          | Inhibit cytotoxicity                                                     | [112]      |
| RvE1 analogs | Decrease transepithelial and endothelial migration. Regulate adhesion molecules. Counteract TNF-α and LTB4 signaling | [73,102,139,185] |
| Macrophages | Enhance effecroticysis                                                  | [33,186]   |
| Platelets   | Reduce aggregation and counter ADP-P2Y12 signaling                       | [138,106]  |
| Osteoclasts | Inhibit bone resorption and cell fusion                                  | [53,106]   |

### RvD1 and analogs

| Target cell | Actions                                                                 | References |
|-------------|--------------------------------------------------------------------------|------------|
| PMN         | Decrease transepithelial and endothelial migration. Regulate adhesion molecules. Counter LB4 and IL-8 actions. Decrease actin remodeling and chemotaxis | [22,39,51] |
| Macrophages | Stimulate effecroticysis. Regulate miRNAs and target genes. enhance killing of bacteria. Promote M2 phenotype and actions | [39,82,106,108] |
| Microglial cells | Inhibit IL-1β.                                                         | [187]      |
| Endothelial cells | Reduce PMN rolling, adhesion, and diapedesis                           | [188]      |
| Vascular Smooth Muscle Cells | Inhibit proliferation, migration, leukocyte adhesion, and pro-inflammatory mediators | [189]      |
| Gingival fibroblasts | Decrease cytokine-induced prostaglandin E2 production while increasing LXA4, Enhances wound healing. | [190]      |
| B lymphocytes | Enhance IgG and IgM production                                           | [191]      |
| Lung fibroblasts and epithelial cells | Decrease IL-6, IL-8, MCP-1, and PGE2 production                          | [192]      |
| RvD2        | PMN Reduces L-selectin shedding and CD18 expression. Inhibit interactions with endothelial cells | [81]       |
function of acute inflammation against external or internal dangers and the need to prevent this reaction from becoming uncontrolled, it is not surprisingly that SPM have some overlapping immunoresolving actions. Further, the sites of biosynthesis for each SPM and the degree of cell distribution of their GPCRs may account for their selectivity and specificity within resolution programs.

The first evidence for receptor-mediated actions of LXA₄ arises from studies by Nigham et al. that demonstrated stimulation of rapid lipid remodeling and pertussis toxin (PTX)-sensitive release of AA in studies by Nigham et al. that demonstrated stimulation of rapid formyl receptor, as putative LXA₄ GPCR [92]. This receptor has been identified in dendritic cells, and resident cells [94]. Orthologous genes of the human high expressed in myeloid cells and at a lower extent in lymphocytes, that radio-labeled 15-epi-LXA₄ binds at cysteinyl LT receptor 1 able to coordinate anti-inflammatory and pro-resolving activities of and its N-terminal peptides [13], representing the prototype of GPCR.

At least two GPCRs are involved in mediating RvE1 actions, namely ChemR23 and BLT1 [73,102]. [³H]-RvE1 bound to ChemR23 transfectants with high affinity (Kᵢ = 11.3 ± 5.4 nM) and stereoselectivity [73]. Also, the synthetic peptide fragment (YH5FFFPGQFAFS) derived from human chemerin that was earlier reported to be a ligand for this same receptor [103] displaced [³H]-RvE1 binding by ~70% when tested at 10 μM concentration, suggesting that RvE1 and chemerin share recognition sites on ChemR23 [73,104]. [³H]-RvE1 specific binding was also demonstrated with membrane fractions isolated from human PMN (Kᵢ of ~50 nM) and was displaced by homologid RvE1 (Kᵢ ~ 34 nM), LTB₄ (Kᵢ = 0.08 nM) and LTB4 receptor 1 (BLT1) selective antagonist U-75302 (Kᵢ = 1.5 nM), but not by the chemerin peptide [102]. These results strikingly demonstrated that RvE1 binding sites are pharmacologically distinct from ChemR23 on human PMN and prompted to investigate whether RvE1 binds to LTB4 receptors. In these studies, [⁹⁶⁷]-RvE1 also gave high affinity binding to recombinant BLT1 (Kᵢ ~ 45 nM) that was competed by unlabeled LTB4 (Kᵢ = 3 nM). In contrast, BLT2-overexpressing cells did not show [⁹⁷⁷]-RvE1 binding at concentrations up to 10 nM. These results clearly demonstrated that RvE1 binds to BLT1 on human PMN and acts as a partial agonist to attenuate LTβ, in coming signals in both mouse and human leukocytes [102]. Human ChemR23 is expressed in brain, kidney, cardiovascular, gastrointestinal, and myeloid tissues [73]. More recently, direct evidence for ligand-receptor interactions of RvE1 and its epimer 18S-RvE1 was provided using ChemR23 and BLT1 β-arrestin cells with EC50 (~ 6.3 pM) lower than that obtained with RvE1 (~0.14 nM). 18S-RvE1 also antagonized LTB4-mediated BLT1 activation with higher potency and efficacy than RvE1 in BLT1 β-arrestin cells [74]. Hence, RvE1 and 18S-RvE1 can share the same site(s) of specific binding to human ChemR23 as well as BLT1.

RvE2 exerts potent and cell-specific bioactivities on human leukocytes [77,78]. Recently, tritium-labeled [⁹⁷⁷]-RvE2 was synthesized and gave comparable Kᵢ (~ 25 nM) with other SPM in isolated human PMN. In addition, using ChemR23 and BLT1 β-arrestin cells RvE2 was found to share, at least in part, receptors with RvE1 [74].

RvD1 also exerts specific bioactivities on human PMN (e.g., PTX-sensitive reduction of F-actin polymerization), did not stimulate Ca²⁺ release, and did not activate cAMP in human PMN [105]. [⁹⁷⁷]-RvD1 prepared by catalytic hydrogenation of synthetic [13,14]-acetylenic RvD1 methyl ester specifically bound to human PMN with high affinity (Kᵢ ~ 0.17 nM) and was displaced by cold RvD1 (100%) and LXA₄ (60%), but not the AnxA1-derived Ac2-12 peptide [105]. [⁹⁷⁷]-RvD1 also showed specific binding with human monocytes [105]. Screening of phylogenetically related GPCR linked to inflammation and chemotaxis in NF-kB-responsive engineered cells demonstrated that
RvD1 significantly reduced TNF-α-induced NF-κB activation in cells overexpressing either the lipoxin receptor ALX/FPR2 and the orphan, GPR32, but not other GPCRs (e.g. BLT1, BLT2, CBR1, GPR-1, FPR, and ChemR23) [105]. Moreover, RvD1 dose-dependently activated ALX/FPR2 and GPR32 in recombinant β-arrestin cells with EC50 in the low picomolar range (EC50 ~ 1.2 pM for ALX/FPR2; 8.8 pM for GPR32) [105]. In comparison, at equimolar concentrations AT-RvD1, RvD1-carboxy-methyl ester, and a metabolically stable analog 17 (R/S)-methyl RvD1-ME, activated both ALX/FPR2 and GPR32 with similar potencies and EC50, whereas the biosynthetic precursor native DHA was not active with GPR32 and ALX/FPR2 [106]. Hence, RvD1, AT-RvD1, and the derivatives carboxy methyl ester and 17(R/S)-RvD1 directly activate ALX/FPR2 and GPR32. Studies with genetically engineered mice and selective receptor antagonists or blocking antibodies confirmed the ALX/FPR2 and GPR32 dependency of immunoresolving actions of RvD1 [31,39,107-114], which involves regulatory mechanisms on transcription factors, microRNAs, and select genes [108]. Human GPR32 was identified in peripheral blood leukocytes and arterial and venous tissues using a cDNA array. It is mostly abundant on PMN, monocytes and macrophages and is also present on vascular endothelial cells [109]. The murine orthologue of GPR32 is currently unknown whereas it exists in chimpanzees. Regulatory mechanisms of GPR32 are unknown, while those of ALX/FPR2 have recently been uncovered [101]. Although specific receptors for RvD2, RvD3 and RvD4 have not yet been uncovered, the stereoselective actions of RvD2 were inhibited by petusiss toxin [81], implicating the involvement of GPCRs. More recently, Chiang et al. showed activation of RvD1-receptor GPR32 is activated by RvD5 with the recombinant human GPR32 [82].

Specific binding of tritium-labeled (N) PD1 was demonstrated with both retinal pigment cells (RPE) and human PMN (Kd ~ 30 pmol/mg of cell protein), although, at high concentration of radio-ligand (> 10 nM), non-specific binding was evident, likely because of the highly hydrophobic nature of this compound. Also, in competition studies, the free acid form of cold (N)PD1 showed 90-100% displacement of radio-labeled (N)PD1, while other structurally related omega-3 fatty acid-derived compounds gave only minimal or no displacement [115].

**Immunoresolving Actions of SPM in Aging-Related Diseases**

**Lipoxins and ATL**

Lipoxins and ATL represent the prototype of immunoresolvents biosynthesized from AA during a lipid mediator (LM) class switching characteristic of self-contained acute inflammatory reactions [12,116]. They were the first class of PUFA-derived autacoids identified that may account for some of the cardioprotective actions noted with dietary supplementation with EPA together with low-dose aspirin [69]. They were the first class of PUFA-derived autacoids identified that may account for some of the cardioprotective actions noted with dietary supplementation with EPA together with low-dose aspirin [69].

RvD1 and AT-RvD1 are potent regulators of inflammatory responses both in human and murine cells. For instance, they stop PMN transendothelial migration and transepithelial migration [52], and regulate endotoxins-induced cytokine production by MФs [140]. In murine zymosan-induced acute peritonitis, RvD1 lowered the Ψmax and shortened the R by ~ 4 h demonstrating the ability to expedite the onset of resolution [106]. Furthermore, microRNA expression analyses from exudate cells demonstrated that RvD1 controls a specific set of pro-resolving miRNAs miR-21, miR-146b, miR-208a, and miR-219 in vivo in a time- and GPCR-dependent manner as part of its immunoresolving actions [106]. Indeed, target mRNAs for the RvD1-GPCR-regulated miRNAs included genes of the NF-kB activation pathway.

Unresolved inflammation is also a hallmark of metabolic diseases, such as obesity and diabetes, and has pathophysiological roles in disease-associated multi-organ dysfunction [129]. Ex vivo studies with adipose tissues explanted from aging mice demonstrated that LXA4 increases the expression of molecules critical in insulin sensitivity (e.g., the glucose transporter GLUT-4 and IRS-1), restores insulin sensitivity in the tissue, and decreases major pro-inflammatory cytokines such as IL-6 while increasing the pro-resolving IL-10 [130]. These studies also demonstrated that LXA4 increases MФ-mediated glucose uptake in vitro [130]. Finally, results from Borgeson, Docherty et al. demonstrate that LXA4, and a synthetic analog modulate inflammation and tissue degeneration in experimental hind-limb ischemia/reperfusion injury [46,129] and diabetic renal fibrosis [131], providing further areas of investigation for pro-resolution therapies in chronic inflammatory diseases.

**E-series resolvins**

Resolvins of the E-series encompasses several molecules. Among them, RvE1 was the first isolated and studied in depth. RvE1 displayed potent stereoselective actions in vivo and with isolated cells (Tables 1 and 2). At nanomolar levels in vitro, RvE1 strikingly reduced human PMN transendothelial migration, dendritic cell migration and interleukin (IL)-12 production [52,73]. In many pre-clinical models of diseases RvE1 displays potent counterregulatory actions that protect against leukocyte-mediated tissue injury and excessive pro-inflammatory responses. For instance, administration of RvE1 in rabbit and mouse models of periodontitis reduces PMN infiltration, prevents loss of connective tissue and bone, and promotes tissue regeneration [104,132,133]. Furthermore, RvE1 protects against oxygen-induced retinopathy [134] and dry-eye syndrome [135,136], a common disorder of the tear film affecting a significant percentage of the old population [137]. Also, recently RvE1 proved to protect myocardium from ischemia-reperfusion injury reducing the size of infarct area [138]. Interestingly, among SPM, RvE1 carries peculiar, ChemR23-mediated, bioactions on leukocytes and platelets, reducing leukocyte rolling to vessels in vivo, regulating adhesion molecules, and blocking adenosine diphosphate-induced aggregation and signaling, which are pivotal steps in thrombus formation [106,139]. Together, these findings provide evidence for specific, GPCR-mediated mechanisms that may account for some of the cardioprotective actions noted with dietary supplementation with EPA together with low-dose aspirin [69].
| SPM | Disease model | Mechanism of action | References |
|-----|---------------|---------------------|------------|
| Lipoxin A4/ATL | Mouse/dermal inflammation | Inhibits neutrophil recruitment and vascular leakage | [95] |
| | Mouse/dorsal air pouch | Inhibits neutrophil recruitment | [118] |
| | Rabbit/periodontitis | Reduces PMN infiltration and prevents connective tissue and bone loss | [120] |
| | Mouse/periodontitis | Inhibits neutrophil recruitment and lymphatic removal of phagocytes | [32,33] |
| | Mouse/asthma | Inhibits airway hyper-responsiveness and pulmonary inflammation; regulates natural killer and type 2 innate cell activation | [122,169] |
| | Mouse/cystic fibrosis | Decreases neutrophilic inflammation, pulmonary bacterial burden and disease severity | [124] |
| | Mouse/schizophrenia/reperfusion (I/R) injury | Attenuates hind-limb I/R-induced lung injury; causes detachment of adherent leukocytes in mesenteric I/R vessels; reduces myocardial infarct size and area at risk in myocardial I/R; diminishes leukocyte recruitment to venules following I/R in a ALX/FPR2 dependent manner | [196-198] |
| | Mouse/cornea inflammation | Accelerates cornea re-epithelialization, limits sequelae of thermal injury (i.e. neovascularization, opacity) and promotes host defense | [199] |
| | Mouse/angiogenesis | Reduces angiogenic phenotype: endothelial cell proliferation and migration | [111] |
| | Mouse/bone marrow transplant (BMT) | Protects against BMT-induced graft- versus-host diseases (GVHD) | [200] |
| | Rat/glomerulonephritis | Reduces leukocyte rolling and adherence; decreases neutrophil recruitment | [201] |
| | Rat/hyperalgesia | Prolongs paw withdraw latency, reducing hyperalgesic index and reduces paw edema | [202,203] |
| | Rat/pleurisy | Shortens the duration of pleural exudation | [163] |
| | Mouse/tumour growth | Suppresses the growth of transplanted tumours in mice; inhibits angiogenesis | [204] |
| | Mouse/allograft rejections | Prevents acute rejection of vascularized cardiac and renal allografts | [205] |
| | Mouse/arthrits | Inhibits oedema formation and PMN influx, reduces TNF-α and LTB4 levels | [206] |
| | Rat/acute pancreatitis | Inhibits oedema formation and PMN influx, reduces TNF-α and LTB4 levels | [207] |
| | Zebrabigsh/mycobacterial infection | Reduces bacterial burden and growth; improves microbial containment by phagocytes | [47] |
| | Rat/sepsis | Increases survival post cecal ligation puncture; reduces cytokine storm due to NF-κB activation; controls bacterial load and enhances MФ recruitment but not phagocytosis | [208] |
| | Human trial/infantile eczema | Reduces the severity and area of eczema and improves the overall quality of life after topical application; shows comparable efficacy and safety than the glucocorticoid mometasone | [209] |
| | Rat/renal fibrosis | Attenuates inflammation, collagen deposition, macrophage infiltration, and apoptosis | [131] |
| | Mouse/cerebral malaria | Reduces brain inflammation and lymphocyte infiltration; enhances survival | [210] |
| | Mouse/Alzheimer’s disease | Reduces NF-κB activation and cytokine production; stimulates recruitment of alternative/anti-inflammatory microglial cells; reduces Aβ amyloid levels | [162] |
| | Mouse/T. gondii infection | Reduces parasite burden in cardiomiocytes; mediates protective effects of low dose aspirin | [211] |
| | Resolvin E1/18R-Rve1 | Mouse/dorsal air pouch | Inhibits neutrophil recruitment | [11] |
| | | Mouse/peritonitis | Inhibits neutrophil recruitment, regulates chemokine/cytokine production and promotes lymphatic removal of phagocytes | [32,33,73] |
| | | Rabbit/periodontitis | Reduces PMN infiltration, prevents connective tissue and bone loss, promotes healing of diseased tissues and promotes regeneration of lost soft tissue and bone | [104,132] |
| | | Mouse/retinopathy | Protects against neovascularization | [134] |
| | | Mouse/collitis | Decreases PMN recruitment and pro-inflammatory gene expression; improves survival and reduces weight loss; favors LPS-Detoxification through induction of intestinal alkaline phosphatase | [86,212,213] |
| | | Mouse/asthma | Reduces IL-23 and IL-6, and increases IFN-γ and LXA4 in lungs to dampen airway inflammation; decreases eosinophil and lymphocyte recruitment | [34,214,215] |
| | | Mouse/obesity | Regulates adipokines and protects against liver steatosis | [145] |
| | | Mouse/inflammatory pain | Inhibits spontaneous pain and heat and mechanical hypersensitivity; attenuates neuropathic pain | [216,217] |
| | | Rat/cardiac ischaemia/reperfusion injury | Reduces infarct size | [138] |
| | | Mouse/allograft rejections | Prevents acute rejection of vascularized cardiac and renal allografts | [206] |
| | | Mouse/dry eye | Promotes tear production, corneal epithelial integrity, and decreases in inflammatory inducible COX-2. Rve1 inhibits keratocyte transformation to myofibroblasts and lowers the number of monocytes/macrophages | [135] |
| | | Mouse/herpes simplex virus | Reduces severity of herpes simplex virus-induced ocular lesions, reduces angiogenesis and stromal keratitis | [149,218] |
| | | Mouse/figure-induced periodontitis | Prevents alveolar bone loss and enhances tissue regeneration; increases osteoprotegerin levels | [133] |
| | | Planaria/tissue regeneration | Stimulates tissue regeneration after surgical head rescision | [219] |
| | | Mouse/pneumonia and acute lung injury | Decreases lung neutrophil infiltration upon acid-induced lung injury and E.coli infection; enhances clearance of bacteria; reduces pro-inflammatory cytokines in lungs; improves survival | [220] |
| | | Mouse/acute lung injury | Reduces leukocyte accumulation induced by E. coli or carrageenan plus myeloperoxidase; enhances PMN apoptosis and their removal by MФs | [221] |
for the biosynthesis of LT and SPM. Interestingly, in experimental

pathway (e.g. IκB kinase and tumor necrosis factor receptor-associated factor 6), cytokines and chemokines (e.g., IL-8, 10, 12, interferon-α and β), programmed cell death 4, a tumor suppressor molecule that acts as a translational repressor of IL-10 [141], and 5-LO, a pivotal enzyme for the biosynthesis of LT and SPM. Interestingly, in experimental

Table 2: Bioactions of SPM in Ageing-Related Inflammatory Diseases.

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renal fibrosis, LXA₄ attenuated the production of pro-fibrotic proteins (e.g., fibronectin, N-cadherin, thrombospondin, and the notch ligand

jagged-1) in cultured human proximal tubular epithelial cells via up-regulation of microRNA let-7c, further indicating the involvement of miRs in the SPM-triggered protective actions in mammals [142]. Along
this line, results from Fredman et al., Li et al. [141,142] demonstrate that delayed resolution of acute peritonitis, triggered by high doses of zymosan A, dysregulates pro-resolving miR-219 expression along with increased LTB₄ and decreased SPM production [143]. Finally, recent studies reveal that miR-466l was temporally regulated in murine exudate leukocytes and controls prostanoid and immunoresolvent biosynthesis during resolution [144], providing novel evidence that miRs play roles in endogenous SPM-driven resolution pathways, whose failure can contribute to the development of chronic inflammation and diseases.

The role of unresolved inflammation, triggered by alterations in the nutrient sensing and regulation mechanisms, in obesity, insulin resistance, and type 2 diabetes (T2D) is widely appreciated [129]. The beneficial effects of SPM from omega-3 RvE1 and PD1 in pre-clinical models of obesity and diabetes have been shown in ob/ob mice, in which both omega-3-enriched diet and RvE1 administration increased expression of genes involved in glucose transport (e.g., GLUT-4) insulin signaling (e.g., IRS-1), and insulin sensitivity (e.g., PPARγ) [145]. Further studies also revealed that RvD1 improves insulin sensitivity, reduces the pro-inflammatory phenotype of adipose tissue macrophages [111], and promotes the repair of diabetic wounds in leptin-receptor deficient mice [40]. Interestingly, RvD1 also enhances the resolution of inflammation in adipose tissue by skewing MΦs towards an anti-inflammatory/pro-resolution phenotype, with decreased pro-inflammatory adipokines in parallel with increased expression of anti-inflammatory genes [146]. Therefore, these results suggest that stimulating resolution with the endogenous immunoresolvent RvD1 could provide a novel therapeutic strategy for treating inflammation-related complications of obesity and obesity-induced diabetes.

**Neuroprotectins**

Biosynthesis of (N) PD1 occurs in neural tissues in response to injury, ischemia-reperfusion, and exposure to β-amyloid peptides from DHA, the most abundant omega-3 PUFA in nervous tissue and retina [83,147,148]. Consistent with its main site of biosynthesis, (N) PD1 carry exquisite tissue-protective and anti-inflammatory action within the brain and the eye (Tables 1 and 2) where inflammation plays key pathophysiological roles in degenerative and ischemic illnesses. For instance, (N) PD1 blocks PMN transmigration across endothelial cells in a stereospecific manner [72] and reduces leukocyte infiltration in animal models of Herpes Virus Simplex-induced stromal keratitis [149]. Interestingly, intracerebroventricular infusion of 17s-HpDHA, a 12/15-LO product of DHA and precursor of SPM, increased levels of (N)PD1 in hippocampus and attenuated neuroinflammation initiated by endotoxins at least in part via its conversion to SPM [150]. In addition, (N) PD1 reduces leukocyte accumulation, NF-κB activation, and COX-2 induction, as well as the size of damaged areas in rats following experimental stroke [83,151], providing novel therapeutic strategies for treating ischemic episodes in old patients. Alzheimer’s disease (AD) is the major cause of dementia in elderly and is determined by accumulation of amyloid Aβ plaques in the brain, which triggers neuroinflammation [152]. In this setting, (N) PD1 is a potent counter-regulator of the inflammatory response in hippocampus of AD mice and primary human neurons. In particular, (N) PD1 reduces expression of Aβ40-42 -triggered expression of pro-inflammatory genes, suppresses Aβ42 peptide shedding by β-secretase-1, shifting the β-amyloid breakdown towards a non amyloidogenic pathway, and protects neurons from apoptosis [153]. Interestingly, recent studies by Medeiros et al. demonstrate that aspirin-triggered 15-epi-LXA₄ also ameliorates AD symptoms in mice, reducing pro-inflammatory mediators and stimulating clearance of Aβ deposits by specialized microglial cells [154]. Together, these results highlight the important protective functions of SPM in nervous system and prompt to investigate their actions in other neurodegenerative diseases.

**Maresins**

Consistent with general SPM actions, both Mar1 and 7S, 14S-diHDHA reduce PMN infiltration in inflamed tissues and enhance MΦ phagocytosis (Table 1). In addition they carry potent, stereospecific actions linked to analgesia and organ repair (Table 2). In particular, Mar1 reduces capsacin-induced transient receptor potential V1 currents in dissociated primary sensory neurons in a PTX-sensitive manner and spontaneous pain behaviors (i.e., flinching/licking) in mice [19].

Further, Mar1, biosynthesized by brown planaria in response to wound, accelerates the repair of damaged tissue [19]. Since chronic inflammation, pain, and tissue degeneration are common signs of aging-related diseases and can cause disability and discomfort, these findings on anti-inflammatory, pain-relieving, and regenerative actions of Mar1 are intriguing.

**Summation and Conclusions**

In summation, the acute inflammatory response is a highly coordinated defensive response and complete resolution is its ideal outcome, whereas unresolved inflammation plays causative roles in chronic, degenerative and metabolic diseases. Resolution of inflammation is an active process governed in part by specialized immunoresolvent lipid-derived chemical mediators or SPM. SPM act in vivo and in vitro to promote the return to homeostasis and their bioactions are highly stereospecific, GPCR-mediated, and exerted at low doses. Results from the first human clinical trial with a resolvin analog are striking and can open new opportunities for resolution pharmacology. It is therefore envisageable that more human trials will be launched in the near future that will help to test the notion that stimulating resolution can improve the way we treat age-related chronic inflammatory diseases.

“Nunc autem visum est mihi de senectute aliquad ad te conscribere”

(Now, I consider appropriate to write for you something about the old age)

Marcus Tullius Cicero (Cato Maior De Senectute, 44 BC)

To my wife and my family.

**Acknowledgement**

The author is supported by the European Union Seventh Framework Programme [FP7/2007-2013] under grant agreement n° 294187 FP7-PEOPLE-CIG-2011 (to A.R.).

**References**

1. Majno G, Isabelle J (2004) Cells, Tissues, and Disease: Principles of General Pathology: Principles of General Pathology, Oxford University Press, USA.
2. Gordon S (2007) The macrophage: past, present and future. Eur J Immunol 37 Suppl 1: S9-17.
3. Rossi AG, The Resolution of Inflammation (Progress in Inflammation Research).
4. Serhan CN, Brain SD, Buckley CD, Gilroy DW, Haslett C, et al. (2007) Resolution of inflammation: state of the art, definitions and terms. FASEB J 21: 325-332.
5. Medzhitov R (2008) Origin and physiological roles of inflammation. Nature 454: 428-435.
Serhan CN, Savill J (2005) Resolution of inflammation: the beginning programs the end. Nat Immunol 6: 1191-1197.

Nathan C, Ding A (2010) Nonresolving inflammation. Cell 140: 871-882.

Serhan CN, Hambeg M, Samuelsson B (1984) Lipoxins: novel series of biologically active compounds formed from arachidonic acid in human leukocytes. Proc Natl Acad Sci U S A 81: 5335-5339.

Serhan CN, Clish CB, Brannon J, Colgan SP, Chiang N, et al. (2000) Novel functional sets of lipid-derived mediators with anti-inflammatory actions generated from omega-3 fatty acids via cyclooxygenase 2-nonsteroidal antiinflammatory drugs and transcellular processing. J Exp Med 192: 1197-1204.

Levy BD, Clish CB, Schmidt B, Gronert K, Serhan CN (2001) Lipid mediator class switching during acute inflammation: signals in resolution. Nat Immunol 2: 612-619.

Perretti M, Chiang N, La M, Fierro IM, Marullo S, et al. (2002) Endogenous lipid- and peptide-derived anti-inflammatory pathways generated with glucocorticoid and aspirin treatment activate the lipoxin A4 receptor. Nat Med 8: 1296-1302.

Perretti M, Flower RJ (2004) Annexin 1 and the biology of the neutrophil. J Leukoc Biol 76: 25-29.

Savill JS, Henson PM, Haslett C (1989) Phagocytosis of aged human neutrophils by macrophages is mediated by a novel charge-sensitive recognition mechanism. J Clin Invest 84: 1518-1527.

Savill JS, Wylie AH, Henson JE, Walport MJ, Henson PM, et al. (1989) Macrophage phagocytosis of ageing neutrophils in inflammation. Programmed cell death in the neutrophil leads to its recognition by macrophages. J Clin Invest 83: 865-875.

Serhan CN, Chiang N, Van Dyke TE (2008) Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. Nat Rev Immunol 8: 349-361.

Gilroy DW, Lawrence T, Perretti M, Rossi AG (2004) Inflammatory resolution: new opportunities for drug discovery. Nat Rev Drug Discov 3: 401-416.

Serhan CN, Dalí J, Karamov S, Choi A, Park CK, et al. (2012) Macrophage resolvins mediating maresin 1 stimulates tissue regeneration and controls pain. FASEB J 26: 1765-1776.

Dalí J, Winkler JW, Colas RA, Armandotit H, Cheng CY, et al. (2013) Resolvin D3 and aspirin-triggered resolvin D3 are potent immunolubemus. Chem Biol 20: 188-201.

Dalí J, Colas RA, Serhan CN (2013) Novel n-3 immunolubemus: structures and actions. Sci Rep 3: 1940.

Kasuga K, Yang R, Porter TF, Agrawal N, Petasis NA, et al. (2008) Rapid appearance of resolvin precursors in inflammatory exudates: novel mechanisms in resolution. J Immunol 181: 8677-8687.

Psychogios N, Hau DD, Peng J, Guo AC, Mandral R, et al. (2011) The human serum metalome. PLoS One 6: e16957.

Weiss GA, Troxler H, Klinke G, Rogler D, Braegger C, et al. (2013) High levels of anti-inflammatory and pro-resolving lipid mediators lipoxins and resolvins and declining docosahexaenoic acid levels in human milk during the first month of anti-inflammatory and pro-resolving lipid mediators lipoxins and resolvins and declining docosahexaenoic acid levels in human milk during the first month of physical exercise increases urinary excretion of lipoxin A4 and related compounds. J Appl Physiol (1985) 94: 2237-2240.

Markworth JF, Vella L, Lingard BS, Tull DL, Rupasinghe TW, et al. (2013) Human inflammatory and resolving lipid mediator responses to resistance exercise and ibuprofen treatment. Am J Physiol Regul Integr Comp Physiol 305: R1281-1286.

Ederer SC, Kumlín M, Björk T, Anggard A, Lindgren JA (1990) Lipoxin formation in human nasal polypos and bronchial tissue. FEBS Lett 272: 25-28.

Brezinski DA, Nesto RW, Serhan CN (1992) Angioplasty triggers intracoronary leukotrienes and lipoxin A4. Impact of aspirin therapy. Circulation 86: 56-63.

Clára J, Serhan CN (1995) Aspirin triggers previously undescribed bioactive eicosanoids by human endothelial cell-leukocyte interactions. Proc Natl Acad Sci U S A 92: 9475-9479.

Chiang N, Bermudez EA, Ridker PM, Hunwitz S, Serhan CN (2004) Aspirin triggers antiinflammatory 15-epi-lipoxin A4 and inhibits thromboxane in a randomized human trial. Proc Natl Acad Sci U S A 101: 15178-15183.

Morris T, Stables M, Hobbs A, de Souza P, Colville-Nash P, et al. (2009) Effects of low-dose aspirin on acute inflammatory responses in humans. J Immunol 183: 2089-2096.

Bannenberg GL, Chiang N, Ariel A, Mair A, Tjonahen E, et al. (2005) Molecular circuits of resolution: formation and actions of resolvins and protectins. J Immunol 174: 4345-4355.

Schwab JM, Chiang N, Mair A, Serhan CN (2007) Resolvin E1 and protectin D1 activate inflammation-resolution programmes. Nature 447: 869-874.

Haworth O, Cernadas M, Yang R, Serhan CN, Levy BD (2008) Resolvin E1 regulates interleukin 23, interferon-gamma and lipoxin A4 to promote the resolution of allergic airway inflammation. Nat Immunol 9: 873-879.

Navarro-Xavier RA, Newson J, Siveira VL, Farrow SN, Gilroy DW, et al. (2010) A new strategy for the identification of novel molecules with targeted proresolution of inflammatory properties. J Immunol 184: 1516-1525.

Norling LV, Perretti M, Cooper D (2009) Endogenous galectins and the control of the host inflammatory response. J Endocrinol 201: 169-184.

Perretti M, Dalí J (2009) Exploiting the Annexin A1 pathway for the development of novel anti-inflammatory therapeutics. Br J Pharmacol 158: 936-946.

Leitch AE, Lucas CD, Marwick JA, Duffin R, Haslett C, et al. (2012) Cyclin-dependent kinases 7 and 9 specifically regulate neutrophil transcription and their inhibition drives apoptosis to promote resolution of inflammation. Cell Death Differ 19: 1950-1961.

Montero-Melendez T, Dalí J, Perretti M (2013) Gene expression signature-based approach identifies a pro-resolving mechanism of action for histone deacetylase inhibitors. Cell Death Differ 20: 567-575.

Tang Y, Zhang MJ, Hellmann J, Kosuri M, Bhatnagar A, et al. (2013) Proresolving therapy for the treatment of delayed healing of diabetic wounds. Diabetes 62: 618-627.

Hecht I, Rong J, Sampaio AL, Hermesh C, Rutledge C, et al. (2009) A novel peptide agonist of fomyl-peptide receptor-like 1 (ALX) displays anti-inflammatory and cardioprotective effects. J Pharmacol Exp Ther 328: 426-434.

Dalí J, Norling LV, Renshaw D, Cooper D, Leung KY, et al. (2008) Annexin 1 mediates the rapid anti-inflammatory effects of neutrophil-derived microparticles. Blood 112: 2512-2519.

Kamaly N, Friedman G, Subramanian M, Gadde S, Pesic A, et al. (2013) Lipoxins and novel 15-epi-lipoxin analogs display potent anti-inflammatory and cardioprotective actions after oral administration. Br J Pharmaco 143: 43-52.

Sun YP, Tjonahen E, Keledjian R, Zhu M, Yang R, et al. (2009) Anti-inflammatory and pro-resolving properties of benzo-lipoxin A(4) analogs. Prostaglandins Leukot Essent Fatty Acids 81: 357-366.

Norling LV, Spite M, Yang R, Flower RJ, Perretti M, et al. (2011) Cutting edge: Humanized nano-proresolving medicines mimic inflammation-resolution and enhance wound healing. J Immunol 186: 5543-5547.

Wu SH, Chen XQ, Liu B, Wu HJ, Dong L (2013) Efficacy and safety of 15(R/S)-methyl-lipoxin A4 in topical treatment of infantile eczema. Br J Dermatol 168: 1075-1082.

Bannenberg G, Moussignac RL, Gronert K, Devchand PR, Schmidt BA, et al. (2004) Lipoxins and novel 15-epi-lipoxin analogs display potent anti-inflammatory actions after oral administration. Br J Pharmacol 143: 43-52.

Sun YP, Tjonahen E, Keledjian R, Zhu M, Yang R, et al. (2009) Anti-inflammatory and pro-resolving properties of benzo-lipoxin A(4) analogs. Prostaglandins Leukot Essent Fatty Acids 81: 357-366.

Gilroy DW, Colville-Nash PR, Willis D, Chivers J, Paul-Clark MJ, et al. (1999) Inducible cyclooxygenase may have anti-inflammatory properties. Nat Med 5: 172-178.

Gasser O, Schifferi JA (2004) Activated polymorphonuclear neutrophils disseminate anti-inflammatory microparticles by ectocytosis. Blood 104: 2543-2548.

Jones CD, Dalí J, Dimisko L, Wong E, Serhan CN, et al. (2012) Microfluidic chambers for monitoring leukocyte trafficking and humanized nano-proresolving medicines interactions. Proc Natl Acad Sci U S A 109: 20560-20565.
51. Serhan CN, Hong S, Gronert K, Colgan SP, Devchand PR, et al. (2002) Resolvins: a family of bioactive products of omega-3 fatty acid transformation circuits initiated by aspirin treatment that counter proinflammation signals. J Exp Med 196: 1025-1037.

52. Sun YP, Oh SF, Uddin J, Yang R, Gotlinger K, et al. (2007) Resolvin D1 and its aspirin-triggered 17R epimer. Stereochemochemical assignments, anti-inflammatory properties, and enzymatic inactivation. J Biol Chem 282: 9323-9334.

53. Serhan CN, Yang R, Martinud K, Kasuga K, Pillai PS, et al. (2009) Maresins: novel macrophage mediators with potent anti-inflammatory and proresolving actions. J Exp Med 206: 15-23.

54. Samuelsson B, Dahlen SE, Lindgren JA, Rouzer CA, Serhan CN (1987) Leukotrienes and lipoxins: structures, biosynthesis, and biological effects. Science 237: 1171-1176.

55. Takano T, Clish CB, Gronert K, Petasis N, Serhan CN (1998) Neutrophil-mediated changes in vascular permeability are inhibited by topical application of aspirin-triggered 15-epi-lipoxin A4 and novel lipoxin B4 stable analogues. J Clin Invest 101: 819-826.

56. Maddox JF, Hachicha M, Takano T, Petasis NA, Fokin VV, et al. (1997) Lipoxin A4 stable analogs are potent mimetics that stimulate human monocytes and TH-1 cells via a G-protein-linked lipoxin A4 receptor. J Biol Chem 272: 6972-6978.

57. Godson C, Mitchell S, Harvey K, Petasis NA, Hogg N, et al. (2000) Cutting edge: lipoxins rapidly stimulate nonphlogistic phagocytosis of apoptotic neutrophils by monocyte-derived macrophages. J Immunol 164: 1663-1667.

58. Gronert K, Gewirtz A, Madara JL, Serhan CN (1998) Identification of a human enterocyte lipoxin A4 receptor that is regulated by interleukin (IL)-13 and interferon gamma and inhibits tumor necrosis factor alpha-induced IL-8 release. J Exp Med 187: 1285-1294.

59. Levy BD, Romano M, Chapman HA, Reilly JJ, Drazin J, et al. (1993) Human alveolar macrophages have 15-lipoxygenase and generate 15(S)-hydroxy-5,8,11,14-eicosatetraenoic acid and lipoxins. J Clin Invest 92: 1572-1579.

60. Romano M (2010) Lipoxin and aspirin-triggered lipoxins. ScientificWorldJournal 10: 1048-1064.

61. Serhan CN, Sheppard KA (1990) Lipoxin formation during human neutrophil-platelet interactions. Evidence for the transformation of leukotriene A4 by platelet 12-lipoxygenase in vitro. J Clin Invest 85: 772-780.

62. Romano M, Serhan CN (1992) Lipoxin generation by permeabilized human platelets. Biochemistry 31: 8269-8277.

63. Bimbaur Y, Ye Y, Lin Y, Freeberg SY, Nishi SP, et al. (2006) Augmentation of myoccardial production of 15-epi-lipoxin-a4 by pioglitazone and atorvastatin in murine brain, human blood, and glial cells. Autacoids in anti-inflammation. J Biol Chem 278: 14677-14687.

64. Serhan CN, Gotlinger K, Hong S, Lu Y, Siegelman J, et al. (2006) Anti-inflammatory actions of neuroprotectin D1/protectin D1 and its natural stereoisomers: assignments of dihydroxy-containing docosatrienes. J Immunol 176: 1848-1859.

65. Arita M, Bianchini F, Alberti J, Shen A, Chiang N, et al. (2005) Stereochemochemical assignment, antiinflammatory properties, and receptor for the omega-3 lipid mediator resolvin E1. J Exp Med 201: 713-722.

66. Oh SF, Pillai PS, Recchiuti A, Yang R, Serhan CN (2011) Pro-resolving actions and stereoselective biosynthesis of 18S E-series resolvins in human leukocytes and murine inflammation. J Clin Invest 121: 569-581.

67. Haas-Stapleton EJ, Lu Y, Hong S, Arita M, Favoreto S, et al. (2007) Candida albicans modulates host defense by biosynthesizing the pro-resolving mediator resolvin E1. PLoS One 2: e1316.

68. Ogawa N, Kobayashi Y (2009) Total synthesis of resolvin E1. Tetrahedron Letters 50: 6079-6082.

69. Oh SF, Dona M, Fredman G, Krishnamoorthy S, Irimia D, et al. (2012) Resolvin E2 formation and impact in inflammation resolution. J Immunol 188: 4527-4534.

70. Tjonahen E, Oh SF, Siegelman J, Elangovan S, Peracchio KB, et al. (2006) Resolvin E2: identification and anti-inflammatory actions: pivotal role of human 5-lipoxygenase in resolvin E series biosynthesis. Chem Biol 13: 1193-1202.

71. Isoye Y, Arita M, Iwamoto R, Urabe D, Todoroki H, et al. (2013) Stereosequential assignment and anti-inflammatory properties of the omega-3 lipid mediator resolvin E3. J Biochem 153: 355-360.

72. Isoye Y, Arita M, Matsueda S, Iwamoto R, Fujihara T, et al. (2012) Identification and structure determination of novel anti-inflammatory mediator resolvin E3, 17,18-dihydroxyeicosapentaenoic acid. J Biol Chem 287: 10525-10534.

73. Spite M, Norling LV, Summers L, Yang R, Cooper D, et al. (2009) Resolvin D2 is a potent regulator of leukocytes and controls microbial sepsis. Nature 461: 1287-1291.

74. Chiang N, Fredman G, Bäckhed F, Oh SF, Vickery T, et al. (2012) Infection regulates pro-resolving mediators that lower antibiotic requirements. Nature 484: 524-528.

75. Marchesselli VL, Hong S, Lukw WJ, Tian XH, Gronert K, et al. (2003) Novel docosanoids inhibit brain ischemia-reperfusion-mediated leukocyte infiltration and pro-inflammatory gene expression. J Biol Chem 278: 43807-43817.

76. Serhan CN, Fredman G, Yang R, Karamov S, Belayev LS, et al. (2011) Novel proresolving aspirin-triggered DHA pathway. Chem Biol 18: 976-987.

77. Freire-de-Lima CG, Xiao YQ, Gardai SJ, Bratton DL, Schiemen WP, et al. (2006) Apoptotic cells, through transforming growth factor-beta, coordinate induce anti-inflammatory and suppress pro-inflammatory eicosanoid and NO synthesis in murine macrophages. J Biol Chem 281: 38376-38384.

78. Ishida T, Yoshida M, Arita M, Nishitani Y, Nishimi S, et al. (2009) Resolvin E1, an endogenous lipid mediator derived from eicosapentaenoic acid, prevents dextran sulfate sodium-induced collitis. Inflamm Bowel Dis 16: 87-95.

79. Dalli J, Zhu M, Vlasenko NA, Deng B, Haeugström JZ, et al. (2013) The novel 13S,14S-epoxy-maresin is converted by human macrophages to maresin 1 (MaR1), inhibits leukotriene A4 hydrolase (LTA4H), and shifts macrophage phenotype. FASEB J 27: 2573-2583.

80. Rogerio AP, Haworth O, Croze R, Oh SF, Uddin M, et al. (2012) Resolvin D1 and aspirin-triggered resolvin D1 promote resolution of allergic airways responses. J Immunol 189: 1983-1991.

81. Recchiuti A (2013) Resolvin D1 and its GPCRs in resolution circuits of inflammation. Prostaglandins Other Lipid Mediat 107: 64-76.

82. Nigam S, Fiore S, Lusciniska FS, Serhan CN (1990) Lipoxin A4 and lipoxin B4 stimulate the release but not the oxygenation of arachidonic acid in human neutrophils: dissociation between lipid remodeling and adhesion. J Cell Physiol 143: 512-523.

83. Fiore S, Ryeeom SW, Weller PF, Serhan CN (1992) Lipoxin recognition sites. Specific binding of labeled lipoxin A4 with human neutrophils. J Biol Chem 267: 16168-16176.

84. Fiore S, Maddox JF, Perez HD, Serhan CN (1994) Identification of a human cDNA encoding a functional high affinity lipoxin A4 receptor. J Exp Med 180: 253-260.

85. Ye RD, Boulay F, Wang JM, Dahlgren C, Gerard C, et al. (2009) International Union of Basic and Clinical Pharmacology. LXIII. Nomenclature for the formyl peptide receptor (FPR) family. Pharmacol Rev 61: 119-161.
93. Chiang N, Serhan CN, Dahlin SE, Drazen JM, Hay DW, et al. (2006) The lipoxin receptor ALX: potent ligand-specific and stereoselective actions in vivo. Pharmacol Rev 58: 463-487.

94. Takano T, Fiore S, Maddox JF, Brady HR, Petasis NA, et al. (1997) Aspirin-triggered 15-epi-lipoxin A4 (LX4A) and LX4A stable analogues are potent inhibitors of acute inflammation: evidence for anti-inflammatory receptors. J Exp Med 185: 1693-1704.

95. Chiang N, Takano T, Arita M, Watanabe S, Serhan CN (2003) A novel rat lipoxin A4 receptor that is conserved in structure and function. Br J Pharmacol 139: 89-98.

96. Gronert K, Martinsson-Niskanen T, Ravasi S, Chiang N, Serhan CN (2001) Selectivity of recombinant human leukotriene D(4), leukotriene B(4), and lipoxin A(4) receptors with aspirin-triggered 15-epi-LXA(4) and regulation of vascular and inflammatory responses. Am J Pathol 158: 3-9.

97. Elmes ME, Clarkson JP, Mahy NJ, Jasani B (1989) Metallothionein and copper in liver disease with copper retention—a histopathological study. J Pathol 158: 131-137.

98. Devchand PR, Arita M, Hongo S, Bannenberg G, Moussignac RL, et al. (2003) Human ALX receptor regulates neutrophil recruitment in transgenic mice: roles in inflammation and host defense. FASEB J 17: 652-659.

99. Dufton N, Hannon R, Brancaleone V, Dali J, Patel HB, et al. (2010) Anti-inflammatory role of the murine formyl-peptide receptor 2: ligand-specific effects on leukocyte responses and experimental inflammation. J Immunol 184: 2811-2819.

100. Morris T, Stables M, Colville-Nash P, Newson J, Bellingan G, et al. (2010) Dichotomy in duration and severity of acute inflammatory responses in humans arising from differentially expressed proresolving pathways. Proc Natl Acad Sci U S A 107: 8842-8847.

101. Simiele F, Recchiuti A, Mattoscio D, De Luca A, Cianci E, et al. (2012) Transcriptional regulation of the human FPR2/ALX gene: evidence of a heritable genetic variant that impairs promoter activity. FASEB J 26: 1323-1333.

102. Arita M, Ohira T, Sun YP, Elangovan S, Chiang N, et al. (2007) Resolvin E1 selectively interacts with leukotriene B4 receptor BLT1 and ChemR23 to regulate inflammation. J Immunol 178: 3912-3917.

103. Wittamer V, Franssen JD, Vulcano M, Mirjofiet JF, Le Poul E, et al. (2003) Specific recruitment of antigen-presenting cells by chemerin, a novel processed ligand from human inflammatory fluids. J Exp Med 198: 977-985.

104. Hasturk H, Kantarci A, Ohira T, Arita M, Ebrahnii N, et al. (2006) RvE1 protects from local inflammation and osteoclast-mediated bone destruction in periodontitis. FASEB J 20: 401-403.

105. Krishnamoorthy S, Recchiuti A, Chiang N, Fredman G, Serhan CN (2012) Resolvin D1 receptor stereoselectivity and regulation of inflammation and proresolving microRNAs. Am J Pathol 180: 2018-2027.

106. Recchiuti A, Krishnamoorthy S, Fredman G, Chiang N, Serhan CN (2011) MicroRNAs in resolution of acute inflammation: identification of novel resolvin D1-miRNA circuits. FASEB J 25: 544-560.

107. Krishnamoorthy S, Recchiuti A, Chiang N, Yacoubian S, Lee CH, et al. (2010) Resolvin D1 binds human phagocytes with evidence for proresolving receptors. Proc Natl Acad Sci U S A 107: 1660-1665.

108. Norling LV, Dali J, Flick LM, Park KW, Softic S, Greer TM, et al. (2004) Defective lipoxin-mediated anti-inflammatory activity in the cystic fibrosis airway. Nat Immunol 5: 388-392.

109. Planagumà A, Kazani S, Marigowda G, Haworth O, Mariani TJ, et al. (2008) Airway lipoxin A4 generation and lipoxin A4 receptor expression are decreased in severe asthma. Am J Respir Crit Care Med 178: 574-582.

110. Mattoscio D, Evangelista V, De Cristofaro R, Recchiuti A, Pandolfi A, et al. (2010) Cystic fibrosis transmembrane conductance regulator (CFTR) expression in human platelets: impact on mediators and mechanisms of the inflammatory response. FASEB J 24: 3970-3980.

111. Cilia S, Nguyen BT, Madenci AL, Ozaki CK, Serhan CN (2013) Diversity of lipid mediators in human adipose tissue depots. Am J Physiol Cell Physiol 304: C1141-1149.

112. Kosicka A, Cunliffe AD, Mackenzie R, Zarwalga M, Perretti M, et al. (2013) Attenuation of plasma annexin A1 in human obesity. FASEB J 27: 369-378.

113. Hotamisligil GS, Ersay B (2008) Nutrient sensing and inflammation in metabolic diseases. Nat Rev Immunol 8: 923-934.

114. Börgesö E, McGiulcuddy FC, Harford KA, Corrigan N, Higgins DF, et al. (2012) Lipoxin A4 attenuates adipose inflammation. FASEB J 26: 4287-4294.

115. Börgesö E, Docherty NG, Murphy M, Rodgers K, Ryan A, et al. (2011) Lipoxin A4, and benzo-lipoxy A4, attenuate experimental renal fibrosis. FASEB J 25: 2967-2979.

116. Hasturk H, Kantarci A, Goguet-Surmenian E, Blackwood A, Andry C, et al. (2007) Resolvin E1 regulates inflammation at the cellular and tissue level and restores tissue homeostasis in vivo. J Immunol 179: 7021-7029.

117. Gao L, Faibish D, Fredman G, Herrera BS, Chiang N, et al. (2013) Resolvin E1 and chemokine-like receptor 1 mediate bone preservation. J Immunol 190: 689-694.

118. Connor KM, SanGiovanni JP, Loftsvist C, Adamson CM, Chen J, et al. (2007) Increased dietary intake of omega-3-polyunsaturated fatty acids reduces pathological retinal angiogenesis. Nat Med 13: 868-873.

119. Li N, He J, Schwartz CE, Gjörup TR, Bazar HE (2010) Resolvin E1 improves tissue repair and decreases inflammation in a dry eye mouse model. J Ocul Pharmacol Ther 26: 431-439.

120. de Paiva CS, Schwartz CE, Gjörup TR, Pflugfelder SC (2012) Resolvin E1
(RX-10001) reduces corneal epithelial barrier disruption and protects against goblet cell loss in a murine model of dry eye. Cornea 31: 1299-1303.

135. Lim LS, Mitchell P, Seddon JM, Holz FG, Wong TY (2012) Age-related macular degeneration. Lancet 379: 1728-1738.

136. Keyes KT, Ye Y, Lin Y, Zhang C, Perez-Polo JR, et al. (2010) Resolin E1 protects the rat heart against reperfusion injury. Am J Physiol Heart Circ Physiol 299: H153-164.

137. Dona M, Fredman G, Schwab JM, Chiang N, Arita M, et al. (2008) Resolin E1, an EPA-derived mediator in whole blood, selectively counterregulates leukocytes and platelets. Blood 112: 648-855.

138. Fredman G, Van Dyke TE, Serhan CN (2010) Resolin E1 regulates adenosine diphosphate activation of human platelets. Arterioscler Thromb Vasc Biol 30: 2005-2013.

139. Merched AJ, Ko K, Gotlinger KH, Serhan CN, Chan L (2008) Atherosclerosis: evidence for impairment of resolution of vascular inflammation governed by specific lipid mediators. FASEB J 22: 3595-3606.

140. Shedly FJ, Palsson-McDermott E, Hennessy EJ, Martin C, O’Leary JY, et al. (2010) Negative regulation of TLR4 via targeting of the proinflammatory tumor suppressor PDCD4 by the microRNA miR-21. Nat Immunol 11: 141-147.

141. Fredman G, Li Y, Dalí J, Chiang N, Serhan CN (2012) Self-limited versus delayed resolution of acute inflammation: temporal regulation of pro-resolving mediators and microRNA. Sci Rep 2: 639.

142. Li Y, Dalí J, Chiang N, Baron RM, Quintana C, et al. (2013) Plasticity of leukocytic exudates in resolving acute inflammation is regulated by MicroRNA and proresolving mediators. Immunity 39: 885-898.

143. González-Pérez A, Horillo R, Ferré N, Gronert K, Dong B, et al. (2009) Oxygen-induced insulin resistance and hepatic steatosis are alleviated by omega-3 fatty acids: a role for resistins and protectins. FASEB J 23: 1946-1957.

144. Titis E, Rius B, González-Pérez A, López-Vicario C, Morán-Salvador E, et al. (2011) Resolin D1 and its precursor docosahexaenoic acid promote resolution of adipose tissue inflammation by eliciting macrophage polarization toward an M2-like phenotype. J Immunol 187: 5408-5418.

145. Mukherjee PK, Marcheselli VL, Serhan CN, Bazan NG (2004) Neuroprotectin D1: a docosahexaenoic acid-derived docosatetraenoic acid promotes human retinal pigment epithelial cells from oxidative stress. Proc Natl Acad Sci U S A 101: 8481-8486.

146. Bazan NG (2007) Homeostatic regulation of photoreceptor cell integrity: significance of the potent mediator neuroprotocin D1 biosynthesized from docosahexaenoic acid: the Proctor Lecture. Invest Ophthalmol Vis Sci 48: 4866-4881.

147. Rajasagi NK, Reddy PB, Mulik S, Gjerstorup P, Rouse BT (2013) Neuroprotocin D1 reduces the severity of herpes simplex virus-induced corneal immunopathology. Invest Ophthalmol Vis Sci 54: 6259-6279.

148. Orr SK, Palumbo S, Bosetti F, Mount HT, Kang JX, et al. (2013) Unesterified docosahexaenoic acid is protective in neuroinflammation. J Neurochem 127: 378-393.

149. Bazan NG, Eady TN, Khourotova L, Atkins KD, Hong S, et al. (2012) Novel aspirin-triggered neuroprotocin D1 attenuates cerebral ischemic injury after experimental stroke. Exp Neurol 236: 122-130.

150. Nussbaum RL, Ellis CE (2003) Alzheimer’s disease and Parkinson’s disease. N Engl J Med 349: 1356-1364.

151. Ramon S, Bancos S, Serhan CN, Phipps RP (2013) Lipoxin A4 modulates adaptive immunity by decreasing memory B-cell responses via an ALX/FPR2-dependent mechanism. Eur J Immunol .

152. Ramstedt U, Ng J, Wiggell H, Serhan CN, Samuelsson B (1985) Action of novel eicosanoids lipoxin A and B on human natural killer cell cytotoxicity: effects on intracellular Ca++ and target cell binding. J Immunol 135: 3434-3438.

153. Ramstedt U, Serhan CN, Nicolau KC, Webber SE, Wiggell H, et al. (1987) Lipoxin A4-inhibited induction of human natural killer cell cytotoxicity: studies on stereospecificity of inhibition and mode of action. J Immunol 138: 266-270.

154. Breziniski ME, Gimbrone MA Jr, Nicolau KC, Serhan CN (1989) Lipoxins stimulate prostanoid generation by human endothelial cells. FEBS Lett 245: 167-172.

155. Cezar-de-Mello PF, Vieira AM, Nascimento-Silva V, Villella CG, Barja-Fidalgo C, et al. (2008) ATL-1, an analogue of aspirin-triggered lipoxin A4, is a potent inhibitor of several steps in angiogenesis induced by vascular endothelial growth factor. Br J Pharmacol 153: 956-965.

156. Nascimento-Silva V, Arruda MA, Barja-Fidalgo C, Fierro IM (2007) Aspirin-triggered lipoxin A4 blocks reactive oxygen species generation in endothelial cells: a novel antioxidative mechanism. Thromb Haemost 97: 88-98.

157. Cezar-de-Mello PF, Nascimento-Silva V, Villella CG, Fierro IM (2006) Aspirin-triggered Lipoxin A4 inhibition of VEGF-induced endothelial cell migration involves actin polymerization and focal adhesion assembly. Oncogene 25: 122-129.

158. Nascimento-Silva V, Arruda MA, Barja-Fidalgo C, Villella CG, Fierro IM (2005) Novel lipid mediator aspirin-triggered lipoxin A4 induces heme oxygenase-1 in endothelial cells. Am J Physiol Cell Physiol 289: C537-563.

159. Fierro IM, Kutok JL, Serhan CN (2002) Novel lipid mediator regulators of endothelial cell proliferation and migration: aspirin-triggered-15R-lipoxin A(4) and Lipoxin A(4). J Pharmacol Exp Ther 300: 385-392.
174. Grumbach Y1, Quynh NV, Chiron R, Urbach V (2009) LX4A stimulates ZO-1 expression and transepithelial electrical resistance in human airway epithelial (16HBE14o-) cells. Am J Physiol Lung Cell Mol Physiol 296: L101-108.

175. Bonnans C, Fukunaga K, Levy MA, Levy BD (2006) Lipoxin A(4) regulates bronchial epithelial cell responses to acid injury. Am J Pathol 168: 1064-1072.

176. Ho KJ, Spite M, Owens CD, Lancero H, Kroemer AH, et al. (2010) Aspirin-triggered lipoxin and resolvin E1 modulate vascular smooth muscle phenotype and correlate with peripheral atherosclerosis. Am J Pathol 177: 2116-2123.

177. Sodin-Senit S, Tadddeo B, Tseng D, Varga J, Fiore S (2000) Lipoxin A4 inhibits IL-1 beta-induced IL-6, IL-8, and matrix metalloproteinase-3 production in human synovial fibroblasts and enhances synthesis of tissue inhibitors of metalloproteinases. J Immunol 164: 2660-2666.

178. Wu SH, Wu XH, Lu C, Dong L, Chen ZQ (2000) Lipoxin A4 inhibits proliferation of human lung fibroblasts induced by connective tissue growth factor. Am J Respir Cell Mol Biol 34: 65-72.

179. Rodgers K, McMahon B, Mitchell D, Sadlier D, Godson G (2005) Lipoxin A4 modifies platelet-derived growth factor-induced pro-fibrotic gene expression in human renal mesangial cells. Am J Pathol 167: 683-694.

180. McMahon B, Mitchell D, Shattuck R, Martin F, Brady HR, et al. (2002) Lipoxin, leukotrienes, and PDGF receptors cross-talk to regulate mesangial cell proliferation. FASEB J 16: 1817-1819.

181. Mitchell D, Rodgers K, Hanly J, McMahon B, Brady HR, et al. (2004) Lipoxin inhibit Akt/PKB activation and cell cycle progression in human mesangial cells. Am J Pathol 164: 937-946.

182. Maddox JF, Colgan SP, Clish CB, Petasis NA, Fokin VV, et al. (1998) Lipoxin B4 regulates human monocyte/neutrophil adherence and motility: design of stable lipoxin B4 analogs with increased biologic activity. FASEB J 12: 487-494.

183. Campbell EL, Louis NA, Tomassetti SE, Canny GO, Arita M, et al. (2007) Resolvin E1 promotes mucus surface clearance of neutrophils: a new paradigm for inflammatory resolution. FASEB J 21: 3162-3170.

184. Ohira T, Arita M, Omori K, Recchiuti A, Van Dyke TE, et al. (2010) Resolvin E1 receptor activation signals phosphorylation and phagocytosis. J Biol Chem 285: 3451-3461.

185. Herrera BS, Ohira T, Gao L, Omori K, Yang R, et al. (2008) An endogenous regulator of inflammation, resolvin E1, modulates osteoclast differentiation and bone resorption. Br J Pharmacol 155: 1214-1223.

186. Zhu M, Van Dyke TE, Gyurko R (2013) Resolvin E1 regulates osteoclast fusion via DC-STAMP and NFATc1. FASEB J 27: 3344-3353.

187. Miyahara S, Taddeo B, Tseng D, Varga J, Fiore S (2000) Lipoxin A4 inhibits IL-1 beta-induced IL-6, IL-8, and matrix metalloproteinase-3 production in human synovial fibroblasts and enhances synthesis of tissue inhibitors of metalloproteinases. J Immunol 164: 2660-2666.

188. Sodin-Senit S, Tadddeo B, Tseng D, Varga J, Fiore S (2000) Lipoxin A4 inhibits IL-1 beta-induced IL-6, IL-8, and matrix metalloproteinase-3 production in human synovial fibroblasts and enhances synthesis of tissue inhibitors of metalloproteinases. J Immunol 164: 2660-2666.

189. Scapinelli MV, Chen B, Sun H, Deng Z, Andersson R, et al. (2013) Protective role of LTA(4H) in mice: the role of antiangiogenesis. Mol Cancer Ther 12: 4321-4329.

190. Chen Y, Hao H, He S, Cai L, Li Y, et al. (2010) Lipoxin A4 and its analogue suppress the tumor growth of transplanted H22 in mice: the role of antiangiogenesis. Mol Cancer Ther 9: 2164-2174.

191. Levy BD, Zhang QY, Bonnans C, Primo V, Reilly JJ, et al. (2011) The endogenous pro-resolving mediators lipoxin A4 and resolvin E1 preserve organ function in allograft rejection. Proc Natl Acad Sci U S A 108: 14398-14403.

192. Arita M, Mao H, Gao F, Serhan CN, Phillips ML, Rennke HG, Brady HR (1995) Specialized pro-resolving mediator lipoxin A(4) and aspirin-triggered lipoxin A(4) protect against experimental cerebral lipoxin A4 operative in murine microcirculation. Blood 96: 501-509.

193. Aoki I, Ikegawa S, Wagerblad G, Bas DB, Codeluppi S, Fernandez-Zafr A, et al. (2013) Spinal actions of lipoxin A4 and 17(R)-resolvin D1 attenuate inflammation-induced mechanical hypersensitivity and spinal TNF release. PLoS One 8: e75543.

194. Chen Y, Hao H, He S, Cai L, Li Y, et al. (2010) Lipoxin A4 and its analogue suppress the tumor growth of transplanted H22 in mice: the role of antiangiogenesis. Mol Cancer Ther 9: 2164-2174.

195. Toh DM, Roca FJ, Oh SF, McFarland R, Vickery TW, et al. (2012) Host genotype-specific therapies can optimize the inflammatory response to mycobacterial infections. Cell 148: 434-446.

196. Walker J, Richter D, Lacorte G, Kerner D, Spur B, et al. (2011) Lipoxin A4 increases survival by decreasing systemic inflammation and bacterial load in sepsis. Shock 36: 410-416.

197. Shroyack N, McBerry C, Salazar Gonzalez RM, James S, Costa FT, et al. (2013) Lipoxin A(4), and 15-epi-lipoxin A(4), protect against experimental cerebral malaria by inhibiting IL-12/IFN-γ in the brain. Prog Neuro-Psychopharmacol Biol Psychiatry 40: 1-12.

198. Morina-Berrios A, Campos-Estrada C, Henriquez N, Faisidez M, Torres G, et al. (2013) Protective role of acetylsalicylic acid in experimental Trypanosoma cruzi infection: evidence of a 15-epi-lipoxin A4-mediated effect. PLoS Negl Trop Dis 7: e2173.

199. Campbell EL, MacManus CF, Kominsky DJ, Keely S, Glover LE, et al. (2010) Resolvin E1-induced intestinal alkaline phosphatase promotes resolution of inflammation through LPS detoxification. PLoS One 5: e115430.

200. Arita M, Yoshida M, Hong S, Tjornahof E, Glickman JN, et al. (2005) Resolvin E1, an endogenous lipid mediator derived from omega-3 eicosapentaenoic acid, protects against 2,4,6-trinitrobenzene sulfonic acid-induced colitis. Proc Natl Acad Sci U S A 102: 7671-7676.

201. Aoki I, Ikegawa S, Wagerblad G, Bas DB, Codeluppi S, Fernandez-Zafr A, et al. (2013) Spinal actions of lipoxin A4 and 17(R)-resolvin D1 attenuate inflammation-induced mechanical hypersensitivity and spinal TNF release. PLoS One 8: e75543.

202. Toh DM, Roca FJ, Oh SF, McFarland R, Vickery TW, et al. (2012) Host genotype-specific therapies can optimize the inflammatory response to mycobacterial infections. Cell 148: 434-446.

203. Walker J, Richter D, Lacorte G, Kerner D, Spur B, et al. (2011) Lipoxin A4 increases survival by decreasing systemic inflammation and bacterial load in sepsis. Shock 36: 410-416.

204. Shroyack N, McBerry C, Salazar Gonzalez RM, James S, Costa FT, et al. (2013) Lipoxin A(4), and 15-epi-lipoxin A(4), protect against experimental cerebral malaria by inhibiting IL-12/IFN-γ in the brain. Prog Neuro-Psychopharmacol Biol Psychiatry 40: 1-12.

205. Morina-Berrios A, Campos-Estrada C, Henriquez N, Faisi dez M, Torres G, et al. (2013) Protective role of acetylsalicylic acid in experimental Trypanosoma cruzi infection: evidence of a 15-epi-lipoxin A4-mediated effect. PLoS Negl Trop Dis 7: e2173.

206. Campbell EL, MacManus CF, Kominsky DJ, Keely S, Glover LE, et al. (2010) Resolvin E1-induced intestinal alkaline phosphatase promotes resolution of inflammation through LPS detoxification. PLoS One 5: e115430.

207. Arita M, Yoshida M, Hong S, Tjornahof E, Glickman JN, et al. (2005) Resolvin E1, an endogenous lipid mediator derived from omega-3 eicosapentaenoic acid, protects against 2,4,6-trinitrobenzene sulfonic acid-induced colitis. Proc Natl Acad Sci U S A 102: 7671-7676.
215. Xu ZZ, Berta T, Ji RR (2013) Resolvin E1 inhibits neuropathic pain and spinal cord microglial activation following peripheral nerve injury. J Neuroimmun Pharmacol 8: 37-41.

216. Rajagasi NK, Reddy PB, Suryawanshi A, Mulik S, Gjorstrup P, et al. (2011) Controlling herpes simplex virus-induced ocular inflammatory lesions with the lipid-derived mediator resolvin E1. J Immunol 186: 1735-1746.

217. Brezinski DA, Serhan CN (1991) Characterization of lipoxins by combined gas chromatography and electron-capture negative ion chemical ionization mass spectrometry: formation of lipoxin A4 by stimulated human whole blood. Biol. Mass Spectrom 20: 45-52.

218. Seki H, Fukunaga K, Arita M, Arai H, Nakanishi H, et al. (2010) The anti-inflammatory and proresolving mediator resolvin E1 protects mice from bacterial pneumonia and acute lung injury. J Immunol 184: 836-843.

219. El Kebir D, Gjorstrup P, Filep JG (2012) Resolvin E1 promotes phagocytosis-induced neutrophil apoptosis and accelerates resolution of pulmonary inflammation. Proc Natl Acad Sci U S A 109: 14983-14988.

220. Kim TH, Kim GD, Jin YH, Park YS, Park CS (2012) Omega-3 fatty acid-derived mediator, Resolvin E1, ameliorates 2,4-dinitrofluorobenzene-induced atopic dermatitis in NC/Nga mice. Int Immunopharmacol 14: 384-391.

221. Spite M, Summers L, Porter TF, Srivastava S, Bhatnagar A, et al. (2009) Resolvin D1 controls inflammation initiated by glutathione-lipid conjugates formed during oxidative stress. Br J Pharmacol 158: 1062-1073.

222. Serhan CN, Chiang N (2008) Endogenous pro-resolving and anti-inflammatory lipid mediators: a new pharmacologic genus. Br J Pharmacol 153 Suppl 1: S200-215.

223. Duffield JS, Hong S, Vaidya VS, Lu Y, Fredman G, et al. (2006) Resolvin D series and protectin D1 mitigate acute kidney injury. J Immunol 177: 5902-5911.

224. Park CK, Xu ZZ, Liu T, Lü N, Serhan CN, et al. (2011) Resolvin D2 is a potent endogenous inhibitor for transient receptor potential potential subtype V1/A1, inflammatory pain, and spinal cord synaptic plasticity in mice: distinct roles of resolvin D1, D2, and E1. J Neurosci 31: 18433-18438.

225. Huang L, Wang CF, Serhan CN, Strichartz G (2011) Enduring prevention and transient reduction of postoperative pain by intrathecal resolvin D1. Pain 152: 557-565.

226. Quan-Xin F, Fan F, Xiang-Ying F, Shu-Jun L, Shi-Qi W, et al. (2012) Resolvin D1 reverses chronic pancreatitis-induced mechanical allodynia, phosphorylation of NMDA receptors, and cytokines expression in the thoracic spinal dorsal horn. BMC Gastroenterol 12: 148.

227. Bang S, Yoo S, Yang TJ, Cho H, Hwang SW (2012) 17(R)-resolvin D1 specifically inhibits transient receptor potential ion channel vanilloid 3 leading to peripheral antinoception. Br J Pharmacol 165: 683-692.

228. Wang B, Gong X, Wan JY, Zhang L, Zhang Z, et al. (2011) Resolvin D1 protects mice from LPS-induced acute lung injury. Pulm Pharmacol Ther 24: 434-441.

229. Jin Y, Arita M, Zhang Q, Saban DR, Chauhan SK, et al. (2009) Anti-angiogenesis effect of the novel anti-inflammatory and pro-resolving lipid mediators. Invest Ophthalmol Vis Sci 50: 4743-4752.

230. Settimonio R, Clara DF, Franca F, Francesca S, Michele D (2012) Resolvin D1 reduces the immunoinflammatory response of the rat eye following uveitis. Mediators Inflamm 2012: 319621.

231. Benito AF, Claudio RF, Dutra RC, Marcon R, Calisto JB (2011) Omega-3 fatty acid-derived mediators 17(R)-hydroxy docosahexaenoic acid, aspirin-triggered resolvin D1 and resolvin D2 prevent experimental colitis in mice. J Immunol 187: 1957-1969.

232. Lima-Garcia JF, Dutra RC, da Silva K, Motta EM, Campos MM, et al. (2011) The precursor of resolvin D series and aspirin-triggered resolvin D1 display anti-hyperalgesic properties in adjuvant-induced arthritis in rats. Br J Pharmacol 164: 278-293.

233. Bohr S, Patel SJ, Sarin D, Trimia D, Yarmush ML, et al. (2013) Resolvin D2 prevents secondary thrombosis and necrosis in a mouse burn wound model. Wound Repair Regen 21: 35-43.

234. Morita M, Kuba K, Ichikawa A, Nakayama M, Katahira J, et al. (2013) The lipid mediator protectin D1 inhibits influenza virus replication and improves severe influenza. Cell 153: 112-125.

235. Levy BD, Kohl P, Gotlinger K, Haworth O, Hong S, et al. (2007) Protectin D1 is generated in asthma and dampens airway inflammation and hyperresponsiveness. J Immunol 178: 496-502.

236. Lukiew J, Bazar NG (2008) Docosahexaenoic acid and the aging brain. J Nutr 138: 2510-2514.

237. Kenchwegowa S, He J, Bazar HE (2013) Involvement of pigment epithelium-derived factor, docosahexaenoic acid and neuroprotectin D1 in corneal inflammation and nerve integrity after refractive surgery. Prostaglandins Leukot Essent Fatty Acids 88: 27-31.

238. Majno G (1991) The Healing Hand Man and Wound in the Ancient World, Harvard University Press.

239. Serhan CN (2011) The resolution of inflammation: the devil in the flask and in the details. FASEB J 25: 1441-1448.