Journal of Gerontology & Geriatric Research

Recchiuti, J Gerontol Geriat Res 2014, 3:2
DOI: 10.4172/2167-7182.1000151

Review Article Open Access

Immunoresolving Lipid Mediators and Resolution of Inflammation in Aging

Antonio Recchiuti*

Department of Clinical and Experimental Sciences, "G. d'Annunzio" University of Chieti and Center of Excellence on Aging (CeSI), Italy

Abstract

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.

Keywords: Neurodegeneration; Inflammatory pathologies; Polymorphonuclear neutrophils

Abbreviations: AA: Arachidonic Acid (5Z, 8Z, 11Z, 14Z - eicosatetraenoic acid); ALX/FPR2: Lipoxin A4 Receptor/Formyl peptide Receptor 2; COX: Cyclooxygenase; DHA: Docosahexaenoic Acid (4Z, 7Z, 10Z, 13Z, 16Z, 19Z - docosahexaenoic acid); EPA: Eicosapentaenoic Acid (5Z, 8Z, 11Z, 14Z, 17Z- eicosapentaenoic acid); GPR32/DRV1: G-Protein Coupled Receptor 32/Resolvin D1 Receptor 1; IκB: Nuclear Factor of κ Light Polypeptide Gene Enhancer in B-cells inhibitor; IL-Interleukin; LM: Lipid Mediator; LO: Lipoxygenase; LX: Lipoxin; Mar: Maresin; (N)PD: (Neuro)Protectin; PG: Prostaglandin; PUFA: Polyunsaturated Fatty Acid; Rv: Resolvin; SPM: Specialized Pro-Resolving Mediator

Acute Inflammation: A Protective Host Response that May Turn into Harm

Acute inflammation is a defensive physiological response occurring in vascularized tissues following injuries or infections [1]. At histological levels, the "cardinal signs" of inflammation were described by the Roman physician Celsus (1st century BC) and are rubor (redness), tumor (swelling), calor (heat), and dolor (pain). These are the macroscopic events tightly regulated at molecular and cellular level in tissues. Edema is one of the earliest event in acute inflammation, arising from increased vascular permeability of the microcirculation (Figure 1). Next, leukocytes, mainly polymorphonuclear neutrophils (PMN), are recruited at sites of inflammation, transmigrate blood vessels linings, and accumulate in the inflamed site to eradicate the cause of inflammation (Figure 1). In experimental acute inflammation monocytes enter the inflammatory site and differentiate into macrophages (MΦs). These latter are pivots in initiating the resolution and the return to homeostasis, i.e. the subsidence of the inflammation and restoration to the previous normal condition, mainly by clearing microbes, cellular debris, and apoptotic cells through non phlogistic phagocytosis (termed efferocytosis) [2-4] and by promoting tissue repair (Figure 1). In order to maintain the host in a healthy status, both the initiation of acute inflammation and its resolution must be efficient. Indeed, impaired acute inflammation will not provide defense against pathogens early post infection [5], while non-resolving inflammation can cause further damage to the host and lead to loss of function, a common feature of many human pathologies including arthritis, asthma, cancers, and cardiovascular diseases [6-8]. Therefore, it is not how often or how extensive an acute inflammatory reaction starts, but how effective and quickly it resolves that determines whether inflammation is detrimental or favorable to the host. Given the high occurrence of inflammation-related diseases in aging, understanding how acute inflammation resolves is of extreme interest.

Microbial infections or tissue damage precipitate an acute inflammatory response in peripheral vascularized tissues, characterized by edema, exudate formation, and leukocyte infiltration. Polymorphonuclear leukocytes (PMN) are among the first leukocytes that infiltrate and fight the pathogenic noxa through engulfment and phagocytosis. Their apoptosis followed by removal initiate tissue resolution. Monocytes that enter the inflamed site as second wave and differentiate into pro-resolving macrophages (MΦs) are master cells in resolution. Activated leukocytes release MPs that can promote resolution. Ancient physicians defined resolving exudates pus bonum et laudabile ("good and laudable pus") as soon as they recognized that it anticipated the resolution of infections and healing of wounds. Today, we appreciate that exudates, in addition to deliver leukocytes in inflamed tissues, also carries bio-precursors for lipoxins, E-series Resolvins, D-series Resolvins, Protectins (neuroprotectin D1), and Maresins,

***Corresponding author:** Antonio Recchiuti, Department of Experimental and Clinical Science and Center of Excellence on Aging (Ce.S.I.), University "G. D'Annunzio" School of Medicine, Via dei Vestini 31, 66013 Chieti, Italy, Tel: +39-0871-541464; Fax: +39-0871-541482L; E-mail: a.recchiuti@unich.it

Received January 21, 2014; **Accepted** March 10, 2014; **Published** March 12, 2014

Citation: Recchiuti A (2014) Immunoresolving Lipid Mediators and Resolution of Inflammation in Aging. J Gerontol Geriat Res 3: 151. doi:10.4172/2167-7182.1000151

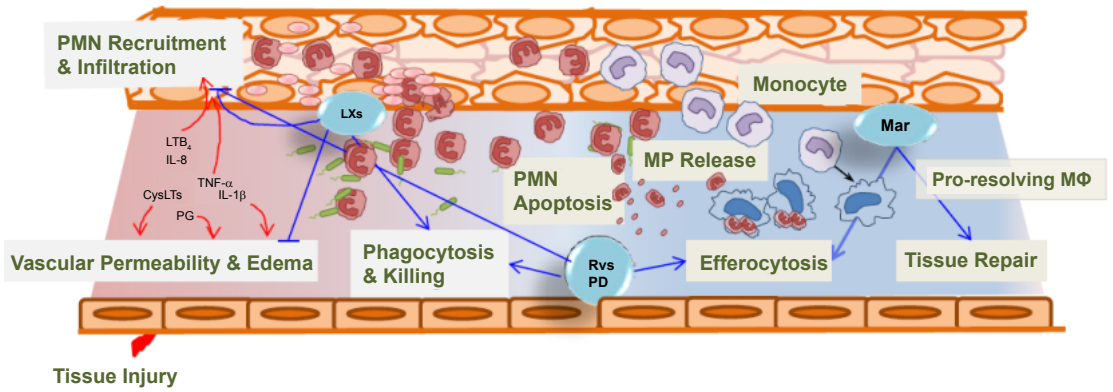

Figure 1: Multistep processes in acute inflammation and resolution. Microbial infections or tissue damage precipitate an acute inflammatory response in peripheral vascularized tissues, characterized by edema, exudate formation, and leukocyte infiltration. Polymorphonuclear leukocytes (PMN) are among the first leukocytes that infiltrate and fight the pathogenic noxa through engulfment and phagocytosis. Their apoptosis followed by removal initiate tissue resolution. Monocytes that enter the inflamed site as second wave and differentiate into pro-resolving macrophages (MΦs) are master cells in resolution. Activated leukocytes release MPs that can promote resolution. Ancient physicians defined resolving exudates *pus bonum et laudabile* ("good and laudable pus") as soon as they recognized that it anticipated the resolution of infections and healing of wounds. Today, we appreciate that exudates, in addition to deliver leukocytes in inflamed tissues, also carries bio-precursors for lipoxins, E-series Resolvins, D-series Resolvins, Protectins (neuroprotectin D1), and Maresins, collectively known as specialized pro-resolving lipid mediators (SPM). SPM work to keep the inflammatory response within physiological boundaries and accelerate the return to homeostasis, providing novel opportunities of therapeutics and treatment of human diseases. For more details on the historical steps that changed our understanding and concepts on the process of resolution of acute inflammation.

collectively known as Specialized Pro-resolving lipid Mediators (SPM). SPM work to keep the inflammatory response within physiological boundaries and accelerate the return to homeostasis, providing novel opportunities of therapeutics and treatment of human diseases. For more details on the historical steps that changed our understanding and concepts on the process of resolution of acute inflammation.

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 MΦ 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 efferocytosis of MΦ (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 lipoxygenase (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 endoperoxydase into a LO–like, initiating the biosynthesis of epimeric forms of SPM, such as 15R-epi- LXA_4 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_{max}, i.e., time point of maximum PMN infiltration (Ψ_{max}); T50, time necessary to achieve 50% reduction in PMN number ($\Psi 50$) from Ψ_{max}; resolution interval (R_i = T50 -T_{max}); time interval between T_{max} and T50 [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 MΦs, 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

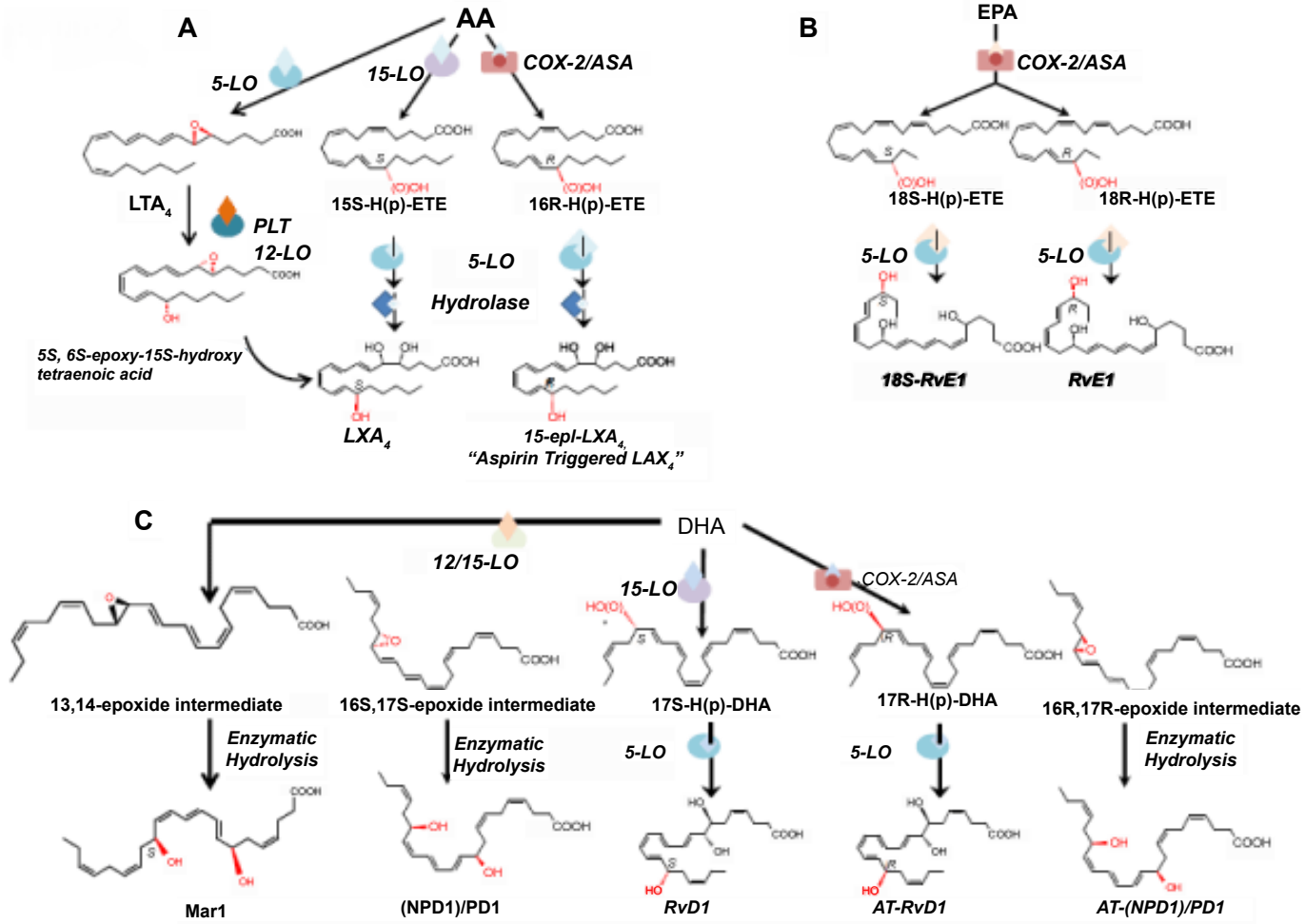

Figure 2: Biosynthesis of endogenous SPM in resolving exudates. Biosynthetic pathways of LXA4, 15-*epi*-LXA4 (A), E-series resolvins (B), D-series resolvins, Maresins, and (neuro)protectins. The complete stereochemistry of each SPM are established, total organic synthesis achieved, and bioactions confirmed. See text and references within for additional details.

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 for 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 MΦ, 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]. LXA_4 and B4 were the first SPM identified by Serhan et al. [9,10]. Although LXs were identified in 1980s in the Samuelsson 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 LXA_4 and B4 in mucosal tissues, such as airways, gastrointestinal tract, and oral cavity [27,59,60] (Figure 2) [61-63]. Blood vessels represent a second site for LX biosynthesis, with the conversion of 5-LO-derived LTA4 into LXA_4 and B4 by 12-LO in platelets [64,65].

ATL: The first aspirin triggered SPM

The ATL synthetic pathway is initiated by aspirin by acetylation of COX-2 which renders the enzyme capable of converting AA into 15R-HETE, the substrate of leukocyte 5-LO for the biosynthesis of positional isomers of LXA_4, named 15R-epi- LXA_4 [29]. This observation proved, for the first time, that aspirin has aspirin has the unique capability, among non-steroidal anti-inflammatory drugs (NSAID), to "jump start" resolution by its ability to trigger endogenous biosynthesis of so called "aspirin triggered" LX (ATL) (Figure 2). In keeping with this, ATL is produced *in vivo* in humans taking aspirin [30] and mediates the local anti-inflammatory actions of low-dose aspirin in healthy individuals [31]. Interestingly, studies from Birnbaum et al. demonstrate that atorvastatin, a widely used lipid-lowering drug, promotes the myocardial generation of 15R -LXA_4 via S-nitrosylation of COX-2 [63]. Furthermore, Gutierrez et al. recently showed that pioglitazone, an insulin-sensitizing agent, elevates plasma levels of 15-epi-LXA_4 [64], providing further mechanisms for the beneficial actions of this drug [65].

E-series resolvins

The essential roles of omega-3 PUFA EPA in health were already evident in 1929 [66] and ω-3 proved beneficial effects in human diseases including potential antithrombotic, immunoregulatory, and antiinflammatory properties [67,68]. Also, the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Prevenzione trial reported a significant~ decrease in cardiovascular death in >11,000 patients surviving myocardial infarction taking 1 g of ω-3 PUFA daily along with recommended preventive treatments including aspirin [69]. However, the mechanisms offered for explaining their beneficial actions (e.g., preventing conversion 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 prostanoids that also maintain antithrombotic 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 PUFA 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 LTA4 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-hydroperoxy, 18-hydroxy-EPE, an intermediate in the biosynthetic pathway of RvE1 [76-78]. Conversely, novel EPA-derived SPM, namely 18R-RvE3 (17R, 18R-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-LO by eosinophils [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 17-hydroxy-containing mediators [53]. Recapitulation of biosynthetic pathways using isolated human 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-HDHA 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 stereochemistry of 17S-, 17R-RvD1, and RvD2 were established as 7S, 8R,17S-trihydroxy-4Z,9E,11E,13Z,15E,19Z-docosahexaenoic acid (17S-RvD1), 7S, 8R, 17R-trihydroxy-4Z,9E,11E,13Z,15E,19Z-docosahexaenoic acid (17R-RvD1) [53], and 7S, 16R, 17S-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-diHDHA, 4S,17S-diHDHA, 7S,17S-diHDHA, and 22-hydrox-10,17S-docosatriene (a putative inactivation product of PD1) [53,72]. Finally, a novel aspirin triggered COX-2 driven pathway that biosynthesize the 17R-epimeric form of PD1 from DHA has been reported [83] (Figure 3). The total organic synthesis and complete streochemical assignment of AT-PD1 (10R,17R- 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

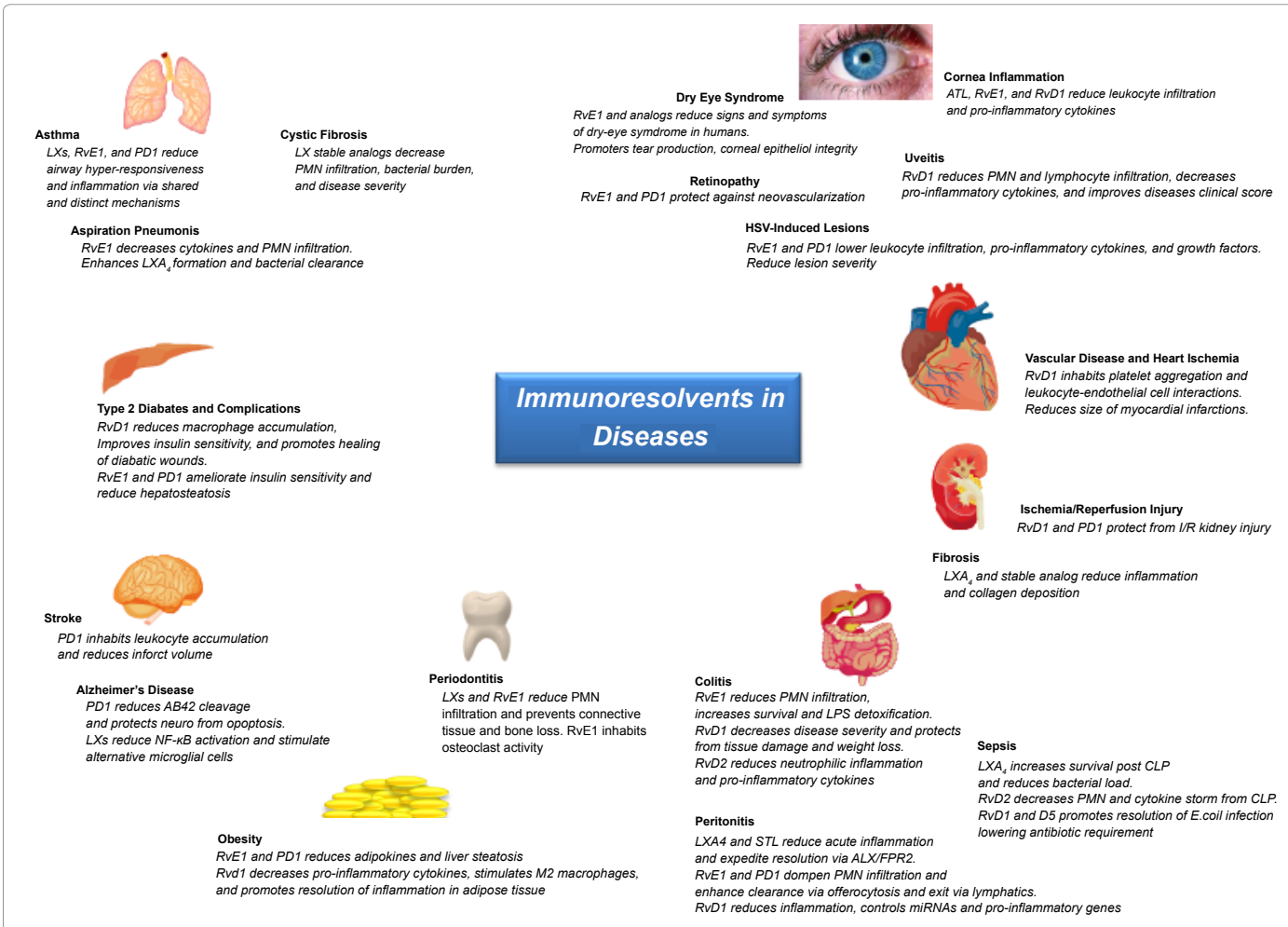

Figure 3: Bioactions of immunoresolvents in diseases. Key multi-pronged anti-inflammatory and pro-resolution actions of SPM in diseases.

example, MΦ ingestion of apoptotic PMN concomitantly initiate tissue resolution [15,16] and the biosynthesis of LXA_4, 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-hydroxydocosaexaenoic 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-epoxide precursor of 7,14-dihydroxydocosa-4Z,8E,10E,12Z,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 double bond geometry and chirality of 13,14-epoxy DHA elucidated together with novel bioactions [87]. These include inhibition of pro-inflammatory LTB4 biosynthesis by LTA4 hydrolase as well AA conversion by 12-LO and regulation of M1/M2 macrophage phenotype (88). In addition to MaR1, a double dioxygenation product, namely 7S, 14S-dihydroxydocosa-4Z,8E,10Z,12E,16Z,19Z-hexaenoic acid (7S,14S-diHDHA), formed by consecutive lipoxygenation of 14-HDHA, was also identified and proved bioactive but less potent than MaR1 in stimulating efferocytosis with human cells [19,54].

GPCRs for SPM in Anti-Inflammation and Resolution

By the definition, SPM: a) are generated within the resolution phase of inflammation; b) limit leukocyte infiltration; c) enhance phagocytic activity of pro-resolving MΦ to remove apoptotic cells and/or microbes; d) stimulate the clearance of PMN from mucosal surfaces and their anti-microbial actions. If a LM carries each of these bioactivities, then it falls into the category of SPM. Beside these general actions, each SPM possesses additional peculiar activities (Table 1). For instance, RvD1 and E1 oppositely regulate interferon γ, LXA_4, and IL-5 in airway exudates during the resolution of allergic inflammation [88] and reviewed in and [89]. In isolated cell systems and experimental models of inflammation and resolution, SPM proved to be active in the nano- to sub micromolar or nano- to low microgram dose range and to act through specific G-protein coupled receptors (GPCRs) in a stereospecific manner (Table 1). Given the important protective

LXA_4 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 eotaxin 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	[167]
NK cells	Block cytotoxicity. Enhance pro-resolution NK-mediated apoptosis of eosinophils and PMN	[112,168,169]
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]
LXB_4 and analogs		
Monocytes	Stimulate non phlogistic recruitment and adhesion	[161,184]
PMN	Inhibit migration and adhesion	[157,184]
NK	Inhibit cytotoxicity	[112]
RvE1 and analogs		
PMN	Decrease transepithelial and endothelial migration. Regulate adhesion molecules. Counteract TNF-α and LTB4 signaling	[73,102,139, 185]
Macrophages	Enhance efferocytosis	[33,186]
Platelets	Reduce aggregation and counter ADP-P2Y12 signaling	[138,106]
Osteoclasts	Inhibit bone resorption and cell fusion	[53,106]
RvD1 and analogs		
PMN	Decrease transepithelial and endothelial migration. Regulate adhesion molecules. Counter LTB4 and IL-8 actions. Decrease actin remodeling and chemotaxis	[22,39,51]
Macrophages	Stimulate efferocytosis. 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 LXA_4. 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]

Macrophages	Stimulates phagocytosis	[81]
Endothelial cells	Activates NO biosynthesis	[81]
Vascular Smooth Muscle Cells	Inhibits proliferation, migration, leukocyte adhesion, and pro-inflammatory mediators	[189]
(N)PD1		
PMN	Enhances CCR5 expression on apoptotic cells	[165]
Macrophages	Stimulates efferocytosis	[33]
Lymphocytes	Blocks chemotaxis and pro-inflammatory genes. Induces apoptosis via lipid raft clustering. Increases CCR5 expression on apoptotic cells during resolution.	[151,165]
Glia cells	Reduces NF-κB activation and COX-2 expression. Represses Aβ42-triggered activation of pro-inflammatory genes while upregulating anti-apoptotic genes	[83,193,194]
Retinal pigment cells	Protects from apoptosis	[195]
Mar1		
Macrophages	Enhances efferocytosis and promotes M2 differentiation	[54,87]

Table 1: Cell-specific bioactions of SPM and stable analogs.

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 LXA_4 arises from studies by Nigham et al. that demonstrated stimulation of rapid lipid remodeling and pertussis toxin (PTX)-sensitive release of AA in PMN treated with LXA_4 [89]. Specific, reversible, and stereoselective binding of synthetic (11,12-^{3}H)-LXA_4 to intact human PMN (with a Kd ~ 0.5 nM) further confirmed the involvement of membrane receptor, likely belonging to the GPCR superfamily, in LXA_4 bioactions [90,91]. Screening of cDNA clones from differentiated HL60 human cells identified formyl peptide receptor like-1, an homologue of formyl receptor, as putative LXA_4 GPCR [92]. This receptor has been renamed ALX/FPR2 in light of its high affinity for LXA_4 [93] and is highly expressed in myeloid cells and at a lower extent in lymphocytes, dendritic cells, and resident cells [94]. Orthologous genes of the human ALX/FPR2 have been identified in rodents [95,96]. In addition to LXA_4, ALX/FPR2 is activated by the glucocorticoid-induced protein AnxA1 and its N-terminal peptides [13], representing the prototype of GPCR able to coordinate anti-inflammatory and pro-resolving activities of both lipid and peptide ligands. While earlier studies demonstrated that radio-labeled 15-epi- LXA_4 binds at cysteinyl LT receptor 1 (CysLT1) with equal affinity to LTD_4, providing additional molecular mechanisms for ATL dampering CysLT signals in the vasculature [97], genetic manipulation of ALX/FPR2 and its orthologue in mice has provided evidence for the essential role of this GPCR in mediating LX actions. Indeed, myeloid-specific overexpression of human ALX/FPR2 in mice resulted in increased sensitivity to suboptimal doses (10 ng/mouse) of the ligand Kstable analog, with >50% reduction in PMN infiltration to zymosan-induced peritonitis compared with <10% reduction in nontransgenic littermates [98]. On the contrary, ALX/FPR2 nullified mice displayed an exacerbated inflammation and delayed resolution phenotype and did not respond to endogenous and synthetic ligands [99]. More strikingly, ATL amounts and ALX/FPR2 expression levels dictate both the magnitude and duration of acute inflammation in humans [100]. Hence, mechanisms that regulate its levels in tissues are of wide interest. In this regard, Simiele et al. recently unraveled the molecular basis of ALX/FPR2 transcriptional machinery, with the identification of the core promoter sequence, the elucidation of transcription factors and epigenetic mechanisms that regulate promoter activity, and the identification of the first inheritable SNP that impairs promoter activity in individuals at high cardiovascular risk [101].

At least two GPCRs are involved in mediating RvE1 actions, namely ChemR23 and BLT1 [73,102]. [^{3}H]-RvE1 bound to ChemR23 transfectants with high affinity (K_d=11.3 ± 5.4 nM) and stereoselectivity [73]. Also, the synthetic peptide fragment (YHSFFFPGQFAFS) derived from human chemerin that was earlier reported to be a ligand for this same receptor [103] displaced [^{3}H]-RvE1 binding by ~70% when tested at 10 μM concentration, suggesting that RvE1 and chemerin share recognition sites on ChemR23 [73,104]. [^{3}H]-RvE1 specific binding was also demonstrated with membrane fractions isolated from human PMN (K_d of ~50 nM) and was displaced by homoligand RvE1 (K_i ~ 34 nM), LTB4 (K_i =0.08 nM) and LTB4 receptor 1 (BLT1) selective antagonist U-75302 (K_i =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, [^{3}H]-RvE1 also gave high affinity binding to recombinant BLT1 (K_d ~ 45 nM) that was competed by unlabeled LTB4 (Ki =3 nM). In contrast, BLT2-overexpressing cells did not show [^{3}H]-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 LTB_4 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 bioactions on human leukocytes [77,78]. Recently, tritium-labeled [^{3}H]-RvE2 was synthesized and gave comparable K_d (~ 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 Ca^{2+} release, and did not activate cAMP in human PMN [105]. [^{3}H]-RvD1 prepared by catalytic hydrogenation of synthetic [13,14]-acetylenic RvD1 methyl ester specifically bound to human PMN with high affinity (Kd ~ 0.17 nM) and was displaced by cold RvD1 (100%) and LXA_4 (~ 60%), but not the AnxA1-derived Ac2-12 peptide [105]. [^{3}H]-RvD1 also showed specific binding with human monocytes [105]. Screening of phylogenetically related GPCR linked to inflammation and chemotaxis in NF-κB-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, CB1, 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 [105]. The murine ortholog 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 petussis 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 to carry dual anti-inflammatory and pro-resolution action, e.g., reducing vascular permeability and inhibiting PMN recruitment to inflammatory loci while stimulating monocytes/MΦs in a non phlogistic manner [57]. LXs undergo *in vivo* rapid inactivation primarily through prostaglandin dehydrogenase-mediated oxidation and reduction [117]. Therefore, several synthetic stable analogs were designed to resist *in vivo* catabolism and proved to carry potent actions *in vivo* and *in vitro* [44-46,118,119] (Tables 1 and 2). Intriguingly, these anti-inflammatory and pro-resolving bioactions do not involve cell toxicity or immunosuppresion, but rather a fine tuning of immune processes. For instance, LXA_4, ATL, stable analogs reduce PMN infiltration and prevents connective tissue and bone loss in a rabbit model of ligature-induced periodontitis [120]. They also attenuate the severity of experimental colitis (diminishing weight loss, inflammation and immune dysfunction) [121], asthma (dampening airway hyper-responsiveness and pulmonary inflammation) [122,123], and cystic fibrosis (decreasing neutrophilic inflammation, pulmonary bacterial burden and disease severity) [124]. Notably, these, and many others, chronic inflammatory diseases present evidence for defective LX-mediated pro-resolution mediators and mechanisms [125-128].

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 LXA_4 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 LXA_4 increases MΦ-mediated glucose uptake *in vitro* [130]. Finally, results from Borgeson, Docherty et al. demonstrate that LXA_4 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 venules *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].

D-series resolvins

RvD1 and AT-RvD1 are potent regulators of inflammatory responses both in human and murine cells. For instance, they stop PMN transendothelial and transepithelial migration [52], and regulate endotoxins-induced cytokine production by MΦs [140]. In murine zymosan-induced acute peritonitis, RvD1 lowered the Ψ_{max} and shortened the R_i 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

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/peritonitis	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/ischaemia/ reperfusion (I/R) injury	Attenuates hind-limb I/R-induced lung injury; causes detachment of adherent leucocytes 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/arthritis	Inhibits oedema formation and PMN influx, reduces TNF-α and LTB_4 levels	[206]
	Rat/acute pancreatitis	Inhibits oedema formation and PMN influx, reduces TNF-α and LTB_4 levels	[207]
	Zebrafish/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 MΦ 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/Toxoplasma gondii infection	Reduces parasite burden in cardiomiocytes; mediates protective effects of low dose aspirin	[211]
Resolvin E1/18*R*-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/colitis	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 LXA_4 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/ligature-induced periodontitis	Prevents alveolar bone loss and enhances tissue regeneration; increases osteoprotegerin levels	[133]
	Planaria/tissue regeneration	Stimulates tissue regeneration after surgical head rescission	[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 MΦs	[221]

	Mouse/atopic dermatitis	Attenuates skin swelling; improves lesions; reduces pro-inflammatory cytokines and leukocyte infiltration	[222]
Resolvin D1/AT-RvD1	Mouse/peritonitis	Inhibits neutrophil recruitment; shortens resolution interval; regulates miRNAs and target genes in resolving exudates; reduces LTB4, PGD2, PGF2α, TXA2 in peritoneal exudates	[53,71,107, 108,188,223]
	Mouse/*E. coli* (peritoneal) and *S. aureus* (skin) infection	Reduces bacterial titres and hypothermia; increased survival; enhances microbial containment and killing by phagocytes; lowers antibiotic requirement; shortens resolution interval	[224]
	Mouse/dorsal air pouch	Inhibits neutrophil recruitment	[52,71,225,226]
	Mouse/kidney ischemia-reperfusion	Protects from ischaemia/reperfusion-induced kidney damage and loss of function; regulates macrophages	[227]
	Mouse/retinopathy	Protects against neovascularization	[134]
	Mouse/inflammatory pain	Inhibits spontaneous pain, heat and mechanical hypersensitivity; selectively blocks TRPV1 and TRPA1-mediated pain	[216,226]
	Mouse/obesity	Reduces inflammatory cytokines in adipose tissue macrophages; stimulates M2 macrophage differentiation; promotes resolution of adipose tissue inflammation	[146]
	Mouse/T2 diabetes	Reduces macrophage accumulation in adipose tissue; ameliorates insulin sensitivity; restores impaired resolution and promotes healing of diabetic wounds	[40,111]
	Rat/post-operative pain	Reduces post-operative pain, tactile allodynia and hyperalgesia	[227]
	Rat/inflammatory pain	Decreases mechanical allodynia in colitis; reduces phosphorylation of NMDA glutamate receptors; does not affect anxiety-like behavior; decreases mechanical hypersensitivity and LPS-evoked TNF-α production	[204,228]
	Mouse/pain	Attenuates agonist-induced and inflammatory pain behaviors; inhibits TRPA1, TRPV3, and TRPV4 receptors; does not affect basal sensitivity	[218,229]
	Mouse/acute lung injury	Blocks leukocyte infiltration and reduces cytokine levels in BALF	[230]
	Mouse/corneal inflammation	Reduces leukocyte infiltration and hemangiogenesis	[231]
	Rat/uveitis	Reduces leukocyte infiltration and cytokine production in LPS-induced uveitis	[232]
	Mouse/colitis	Reduces disease activity index, PMN number, and pro-inflammatory levels	[233]
	Mouse/pain	Attenuates pain signals and behaviors by blocking TRPV3	[234]
	Rats/arthritic pain	Possesses anti-hyperalgesic effects upon systemic administration. Decreases TNF-α and IL-1β production	[235]
	Mouse/ temporomandibular joint inflammation	Reduces complete Freund's adjuvant-induced neutrophil infiltration	[47]
Resolvin D2	Mouse/peritonitis	Blocks further PMN infiltration into the peritoneum	[81]
	Mouse/sepsis	Prevents hypothermia, decreases bacterial load in the blood and peritoneum, promotes survival	[81]
	Mouse/colitis	Improves disease activity index, weight loss, and colonic PMN infiltration. Reduces pro-inflammatory levels	[233]
	Mouse/burn wound	Reduces thrombosis of the deep dermal blood vessels; prevents and subsequent dermal necrosis; decreases PMN-mediated tissue damage	[235]
(Neuro) Protectin D1/AT-PD1	Mouse/peritonitis	Inhibits neutrophil recruitment and regulates chemokine/cytokine production. Promotes lymphatic removal of phagocytes; regulates T-cell migration; enhance CCR5 expression on apoptotic leukocytes	[32,33,72,152,165]
	Mouse/Influenza	Inhibits virus replication and improved the survival and pathology of severe influenza	[236]
	Mouse/asthma	Protects from lung damage, airway inflammation and hyper-responsiveness	[237]
	Human/asthma	PD1 is generated in human asthmatic patients	[238]
	Mouse/kidney ischaemia/ reperfusion	Protects from ischaemia/reperfusion-induced kidney damage and loss of function; regulates macrophages	[226]
	Mouse/retinopathy	Protects against neovascularization	[134]
	Rat/ischemic stroke	Inhibits leukocyte infiltration, NF-κB and COX-2 induction; reduces infarct volumes	[83,152]
	Human/Alzheimer's disease	Diminished PD1 production in human Alzheimer's disease	[238]
	Mouse/liver injury	Protects necro-inflammatory liver injury	[145]
	Mouse/Alzheimer's disease	Down-regulates inflammatory genes; reduces amyloidogenic Aβ42 cleavage; protects from apoptosis	[153]
	Rabbit/corneal damage	Promotes nerve regeneration after surgical damage; reduces inflammation	[239]
	Mouse/ herpes simplex virus (HSV)-induced stromal keratitis (SK)	Lowers infiltration of PMN and CD4+; diminishes the production of proinflammatory cytokines, chemokines, and angiogenic factors	[149]
Maresin-1	Mouse/peritonitis	Blocks PMN infiltration into the peritoneum	[54]
	Planaria/tissue regeneration	Stimulates tissue regeneration post surgical damage	[219]
	Mouse/ pain	Reduces pain	[219]

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

pathway (e.g. IkB 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 renal fibrosis, LXA_4 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 microRNA and lipid mediator profiles, namely with decreased miR-219 expression along with increased LTB_4 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 Aβ-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*-LXA_4 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 capsaicin-induced transient receptor potential V1 currents in dissociated primary sensory in 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 aliquid 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.

6. Serhan CN (2004) A search for endogenous mechanisms of anti-inflammation uncovers novel chemical mediators: missing links to resolution. Histochem Cell Biol 122: 305-321.

7. Serhan CN, Savill J (2005) Resolution of inflammation: the beginning programs the end. Nat Immunol 6: 1191-1197.

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

9. Serhan CN, Hamberg 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.

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

11. 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.

12. 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.

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

14. 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.

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

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

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

18. Serhan CN, Dalli J, Karamnov S, Choi A, Park CK, et al. (2012) Macrophage proresolving mediator maresin 1 stimulates tissue regeneration and controls pain. FASEB J 26: 1755-1765.

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

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

21. 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.

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

23. 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 lactation. Lipids Health Dis 12: 89.

24. Gangemi S, Luciotti G, D'Urbano E, Mallamace A, Santoro D, et al. (2003) Physical exercise increases urinary excretion of lipoxin A4 and related compounds. J Appl Physiol (1985) 94: 2237-2240.

25. 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: R1281-1296.

26. Edenius C, Kumlin M, Björk T, Anggård A, Lindgren JA (1990) Lipoxin formation in human nasal polyps and bronchial tissue. FEBS Lett 272: 25-28.

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

28. Clària 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.

29. Chiang N Bermudez EA, Ridker PM, Hurwitz 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.

30. 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.

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

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

33. 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.

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

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

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

37. 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.

38. Montero-Melendez T, Dalli 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.

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

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

41. Dalli 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.

42. Kamaly N, Fredman G, Subramanian M, Gadde S, Pesic A, et al. (2013) Development and in vivo efficacy of targeted polymeric inflammation-resolving nanoparticles. Proc Natl Acad Sci U S A 110: 6506-6511.

43. Guilford WJ, Bauman JG, Skuballa W, Bauer S, Wei GP, et al. (2004) Novel 3-oxa lipoxin A4 analogues with enhanced chemical and metabolic stability have anti-inflammatory activity in vivo. J Med Chem 47: 2157-2165.

44. 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.

45. 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.

46. 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.

47. Wu SH, Chen XQ, Liu B, Wu HJ, Dong L (2013) Efficacy and safety of 15(R/S)-methyl-lipoxin A(4) in topical treatment of infantile eczema. Br J Dermatol 168: 172-178.

48. 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: 698-701.

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

50. Jones CN, Dalli 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. Stereochemical assignments, anti-inflammatory properties, and enzymatic inactivation. J Biol Chem 282: 9323-9334.

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

54. Samuelsson B, Dahlén 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 THP-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, Drazen J, et al. (1993) Human alveolar macrophages have 15-lipoxygenase and generate 15(S)-hydroxy-5,8,11-cis-13-trans-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. Birnbaum Y, Ye Y, Lin Y, Freeberg SY, Nishi SP, et al. (2006) Augmentation of myocardial production of 15-epi-lipoxin-a4 by pioglitazone and atorvastatin in the rat. Circulation 114: 929-935.

64. Gutierrez AD, Sathyanarayana P, Konduru S, Ye Y, Birnbaum Y, et al. (2012) The effect of pioglitazone treatment on 15-epi-lipoxin A4 levels in patients with type 2 diabetes. Atherosclerosis 223: 204-208.

65. Burr GO, Burr MM (1973) Nutrition classics from The Journal of Biological Chemistry 82:345-67, 1929. A new deficiency disease produced by the rigid exclusion of fat from the diet. Nutr Rev 31: 248-249.

66. De Caterina R (2011) n-3 fatty acids in cardiovascular disease. N Engl J Med 364: 2439-2450.

67. Iigo M, Nakagawa T, Ishikawa C, Iwahori Y, Asamoto M, et al. (1997) Inhibitory effects of docosahexaenoic acid on colon carcinoma 26 metastasis to the lung. Br J Cancer 75: 650-655.

68. (1999) Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet 354: 447-455.

69. Calder PC (2009) Polyunsaturated fatty acids and inflammatory processes: New twists in an old tale. Biochimie 91: 791-795.

70. Hong S, Gronert K, Devchand PR, Moussignac RL, Serhan CN (2003) Novel docosatrienes and 17S-resolvins generated from docosahexaenoic acid in murine brain, human blood, and glial cells. Autacoids in anti-inflammation. J Biol Chem 278: 14677-14687.

71. 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.

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

73. 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.

74. 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.

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

76. 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.

77. Tjonahen E, Oh SF, Siegelman J, Elangovan S, Percarpio 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.

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

79. Isobe 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.

80. 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.

81. 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.

82. Marcheselli VL, Hong S, Lukiw 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.

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

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

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

86. Dalli J, Zhu M, Vlasenko NA, Deng B, Haeggström 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.

87. 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.

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

89. Nigam S, Fiore S, Luscinskas FW, 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.

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

91. 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.

92. Ye RD, Boulay F, Wang JM, Dahlgren C, Gerard C, et al. (2009) International Union of Basic and Clinical Pharmacology. LXXIII. Nomenclature for the formyl peptide receptor (FPR) family. Pharmacol Rev 61: 119-161.

93. Chiang N, Serhan CN, Dahlén 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 (LXA4) and LXA4 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, Hong 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, Dalli 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: 2611-2619.

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 proresolution 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, Mirjolet 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, Ebrahimi 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, Dalli J, Flower RJ, Serhan CN, Perretti M (2012) Resolvin D1 limits polymorphonuclear leukocyte recruitment to inflammatory loci: receptor-dependent actions. Arterioscler Thromb Vasc Biol 32: 1970-1978.

109. Hellmann J, Tang Y, Kosuri M, Bhatnagar A, Spite M (2011) Resolvin D1 decreases adipose tissue macrophage accumulation and improves insulin sensitivity in obese-diabetic mice. FASEB J 25: 2399-2407.

110. Lee HN, Surh YJ (2013) Resolvin D1-mediated NOX2 inactivation rescues macrophages undertaking efferocytosis from oxidative stress-induced apoptosis. Biochem Pharmacol 86: 759-769.

111. Buchanan PJ, McNally P, Harvey BJ, Urbach V (2013) Lipoxin Aâ„-mediated KATP potassium channel activation results in cystic fibrosis airway epithelial repair. Am J Physiol Lung Cell Mol Physiol 305: L193-201.

112. Barnig C, Cernadas M, Dutile S, Liu X, Perrella MA, et al. (2013) Lipoxin A4 regulates natural killer cell and type 2 innate lymphoid cell activation in asthma. Sci Transl Med 5: 174ra26.

113. Gavins FN, Hughes EL, Buss NA, Holloway PM, Getting SJ, et al. (2012) Leukocyte recruitment in the brain in sepsis: involvement of the annexin 1-FPR2/ALX anti-inflammatory system. FASEB J 26: 4977-4989.

114. Marcheselli VL, Mukherjee PK, Arita M, Hong S, Antony R, et al. (2010) Neuroprotectin D1/protectin D1 stereoselective and specific binding with human retinal pigment epithelial cells and neutrophils. Prostaglandins Leukot Essent Fatty Acids 82: 27-34.

115. Serhan CN, Maddox JF, Petasis NA, Akritopoulou-Zanze I, Papayianni A, et al. (1995) Design of lipoxin A4 stable analogs that block transmigration and adhesion of human neutrophils. Biochemistry 34: 14609-14615.

116. Clish CB, O'Brien JA, Gronert K, Stahl GL, Petasis NA, et al. (1999) Local and systemic delivery of a stable aspirin-triggered lipoxin prevents neutrophil recruitment in vivo. Proc Natl Acad Sci U S A 96: 8247-8252.

117. Petasis NA, Akritopoulou-Zanze I, Fokin VV, Bernasconi G, Keledjian R, et al. (2005) Design, synthesis and bioactions of novel stable mimetics of lipoxins and aspirin-triggered lipoxins. Prostaglandins Leukot Essent Fatty Acids 73: 301-321.

118. Serhan CN, Jain A, Marleau S, Clish C, Kantarci A, et al. (2003) Reduced inflammation and tissue damage in transgenic rabbits overexpressing 15-lipoxygenase and endogenous anti-inflammatory lipid mediators. J Immunol 171: 6856-6865.

119. Gewirtz AT, Neish AS, Madara JL (2002) Mechanisms of active intestinal inflammation and potential down-regulation via lipoxins. Adv Exp Med Biol 507: 229-236.

120. Levy BD, De Sanctis GT, Devchand PR, Kim E, Ackerman K, et al. (2002) Multi-pronged inhibition of airway hyper-responsiveness and inflammation by lipoxin A(4). Nat Med 8: 1018-1023.

121. Levy BD, Lukacs NW, Berlin AA, Schmidt B, Guilford WJ, et al. (2007) Lipoxin A4 stable analogs reduce allergic airway responses via mechanisms distinct from CysLT1 receptor antagonism. FASEB J 21: 3877-3884.

122. Karp CL, 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.

123. 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.

124. 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.

125. Clària J, 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.

126. Kosicka A, Cunliffe AD, Mackenzie R, Zariwala MG, Perretti M, et al. (2013) Attenuation of plasma annexin A1 in human obesity. FASEB J 27: 368-378.

127. Hotamisligil GS, Erbay E (2008) Nutrient sensing and inflammation in metabolic diseases. Nat Rev Immunol 8: 923-934.

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

129. Börgeson E, Docherty NG, Murphy M, Rodgers K, Ryan A, et al. (2011) Lipoxin Aâ„ and benzo-lipoxin Aâ„ attenuate experimental renal fibrosis. FASEB J 25: 2967-2979.

130. 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.

131. 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.

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

133. Li N, He J, Schwartz CE, Gjorstrup P, Bazan HE (2010) Resolvin E1 improves tear production and decreases inflammation in a dry eye mouse model. J Ocul Pharmacol Ther 26: 431-439.

134. de Paiva CS, Schwartz CE, Gjörstrup P, 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) Resolvin 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) Resolvin E1, an EPA-derived mediator in whole blood, selectively counterregulates leukocytes and platelets. Blood 112: 848-855.

138. Fredman G, Van Dyke TE, Serhan CN (2010) Resolvin 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. Sheedy FJ, Palsson-McDermott E, Hennessy EJ, Martin C, O'Leary JJ, 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, Dalli 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, Dalli 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-Périz A, Horrillo R, Ferré N, Gronert K, Dong B, et al. (2009) Obesity-induced insulin resistance and hepatic steatosis are alleviated by omega-3 fatty acids: a role for resolvins and protectins. FASEB J 23: 1946-1957.

144. Titos E, Rius B, González-Périz A, López-Vicario C, Morán-Salvador E, et al. (2011) Resolvin 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 docosatriene protects human retinal pigment epithelial cells from oxidative stress. Proc Natl Acad Sci U S A 101: 8491-8496.

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

147. Rajasagi NK, Reddy PB, Mulik S, Gjorstrup P, Rouse BT (2013) Neuroprotectin D1 reduces the severity of herpes simplex virus-induced corneal immunopathology. Invest Ophthalmol Vis Sci 54: 6269-6279.

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, Khoutorova L, Atkins KD, Hong S, et al. (2012) Novel aspirin-triggered neuroprotectin 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 348: 1356-1364.

151. Zhao Y, Calon F, Julien C, Winkler JW, Petasis NA, et al. (2011) Docosahexaenoic acid-derived neuroprotectin D1 induces neuronal survival via secretase- and PPARÎ³-mediated mechanisms in Alzheimer's disease models. PLoS One 6: e15816.

152. Medeiros R, Kitazawa M, Passos GF, Baglietto-Vargas D, Cheng D, et al. (2013) Aspirin-triggered lipoxin A4 stimulates alternative activation of microglia and reduces Alzheimer disease-like pathology in mice. Am J Pathol 182: 1780-1789.

153. Fiore S, Serhan CN (1995) Lipoxin A4 receptor activation is distinct from that of the formyl peptide receptor in myeloid cells: inhibition of CD11/18 expression by lipoxin A4-lipoxin A4 receptor interaction. Biochemistry 34: 16678-16686.

154. József L, Zouki C, Petasis NA, Serhan CN, Filep JG (2002) Lipoxin A4 and aspirin-triggered 15-epi-lipoxin A4 inhibit peroxynitrite formation, NF-kappa B and AP-1 activation, and IL-8 gene expression in human leukocytes. Proc Natl Acad Sci U S A 99: 13266-13271.

155. Papayianni A, Serhan CN, Brady HR (1996) Lipoxin A4 and B4 inhibit leukotriene-stimulated interactions of human neutrophils and endothelial cells. J Immunol 156: 2264-2272.

156. Levy BD, Fokin VV, Clark JM, Wakelam MJ, Petasis NA, et al. (1999) Polyisoprenyl phosphate (PIPP) signaling regulates phospholipase D activity: a 'stop' signaling switch for aspirin-triggered lipoxin A4. FASEB J 13: 903-911.

157. Börgeson E, Lönn J, Bergström I, Brodin VP, Ramström S, et al. (2011) Lipoxin A(4) inhibits porphyromonas gingivalis-induced aggregation and reactive oxygen species production by modulating neutrophil-platelet interaction and CD11b expression. Infect Immun 79: 1489-1497.

158. Carlo T, Kalwa H, Levy BD (2013) 15-Epi-lipoxin A4 inhibits human neutrophil superoxide anion generation by regulating polyisoprenyl diphosphate phosphatase 1. FASEB J 27: 2733-2741.

159. Maddox JF, Serhan CN (1996) Lipoxin A4 and B4 are potent stimuli for human monocyte migration and adhesion: selective inactivation by dehydrogenation and reduction. J Exp Med 183: 137-146.

160. Mitchell D, O'Meara SJ, Gaffney A, Crean JK, Kinsella BT, et al. (2007) The Lipoxin A4 receptor is coupled to SHP-2 activation: implications for regulation of receptor tyrosine kinases. J Biol Chem 282: 15606-15618.

161. Bandeira-Melo C, Serra MF, Diaz BL, Cordeiro RS, Silva PM, et al. (2000) Cyclooxygenase-2-derived prostaglandin E2 and lipoxin A4 accelerate resolution of allergic edema in Angiostrongylus costaricensis-infected rats: relationship with concurrent eosinophilia. J Immunol 164: 1029-1036.

162. Soyombo O, Spur BW, Lee TH (1994) Effects of lipoxin A4 on chemotaxis and degranulation of human eosinophils stimulated by platelet-activating factor and N-formyl-L-methionyl-L-leucyl-L-phenylalanine. Allergy 49: 230-234.

163. Ariel A, Fredman G, Sun YP, Kantarci A, Van Dyke TE, et al. (2006) Apoptotic neutrophils and T cells sequester chemokines during immune response resolution through modulation of CCR5 expression. Nat Immunol 7: 1209-1216.

164. Ariel A, Chiang N, Arita M, Petasis NA, Serhan CN (2003) Aspirin-triggered lipoxin A4 and B4 analogs block extracellular signal-regulated kinase-dependent TNF-alpha secretion from human T cells. J Immunol 170: 6266-6272.

165. 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 .

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

167. Ramstedt U, Serhan CN, Nicolaou KC, Webber SE, Wigzell H, et al. (1987) Lipoxin A-induced inhibition of human natural killer cell cytotoxicity: studies on stereospecificity of inhibition and mode of action. J Immunol 138: 266-270.

168. Brezinski ME, Gimbrone MA Jr, Nicolaou KC, Serhan CN (1989) Lipoxins stimulate prostacyclin generation by human endothelial cells. FEBS Lett 245: 167-172.

169. Cezar-de-Mello PF, Vieira AM, Nascimento-Silva V, Villela 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.

170. 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.

171. Cezar-de-Mello PF, Nascimento-Silva V, Villela 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.

172. Nascimento-Silva V, Arruda MA, Barja-Fidalgo C, Villela CG, Fierro IM (2005) Novel lipid mediator aspirin-triggered lipoxin A4 induces heme oxygenase-1 in endothelial cells. Am J Physiol Cell Physiol 289: C557-563.

173. 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) LXA4 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-Semrl 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.

178. Wu SH, Wu XH, Lu C, Dong L, Chen ZQ (2006) 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 C (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, Shattock R, Martin F, Brady HR, et al. (2002) Lipoxin, leukotriene, 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) Lipoxins 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 mucosal 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 T, Runge S, Chatterjee A, Chen M, Mottola G, et al. (2013) D-series resolvin attenuates vascular smooth muscle cell activation and neointimal hyperplasia following vascular injury. The FASEB J 27: 2220-2232.

188. Mustafa M, Zarrough A, Bolstad AI, Lygre H, Mustafa K, et al. (2013) Resolvin D1 protects periodontal ligament. Am J Physiol Cell Physiol 305: C673-679.

189. Ramon S, Gao F, Serhan CN, Phipps RP (2012) Specialized proresolving mediators enhance human B cell differentiation to antibody-secreting cells. J Immunol 189: 1036-1042.

190. Hsiao HM, Sapinoro RE, Thatcher TH, Croasdell A, Levy EP, et al. (2013) A novel anti-inflammatory and pro-resolving role for resolvin D1 in acute cigarette smoke-induced lung inflammation. PLoS One 8: e58258.

191. Ariel A, Li PL, Wang W, Tang WX, Fredman G, et al. (2005) The docosatriene protectin D1 is produced by TH2 skewing and promotes human T cell apoptosis via lipid raft clustering. J Biol Chem 280: 43079-43086.

192. Lukiw WJ, Cui JG, Marcheselli VL, Bodker M, Botkjaer A, et al. (2005) A role for docosahexaenoic acid-derived neuroprotectin D1 in neural cell survival and Alzheimer disease. J Clin Invest 115: 2774-2783.

193. Antony R, Lukiw WJ, Bazan NG (2010) Neuroprotectin D1 induces dephosphorylation of Bcl-xL in a PP2A-dependent manner during oxidative stress and promotes retinal pigment epithelial cell survival. J Biol Chem 285: 18301-18308.

194. Chiang N, Gronert K, Clish CB, O'Brien JA, Freeman MW, et al. (1999) Leukotriene B4 receptor transgenic mice reveal novel protective roles for lipoxins and aspirin-triggered lipoxins in reperfusion. J Clin Invest 104: 309-316.

195. Scalia R, Gefen J, Petasis NA, Serhan CN, Lefer AM (1997) Lipoxin A4 stable analogs inhibit leukocyte rolling and adherence in the rat mesenteric microvasculature: role of P-selectin. Proc Natl Acad Sci U S A 94: 9967-9972.

196. Brancaleone V, Gobbetti T, Cenac N, le Faouder P, Colom B, et al. (2013) A vasculo-protective circuit centered on lipoxin A4 and aspirin-triggered 15-epi-lipoxin A4 operative in murine microcirculation. Blood 122: 608-617.

197. Gronert K, Maheshwari N, Khan N, Hassan IR, Dunn M, et al. (2005) A role for the mouse 12/15-lipoxygenase pathway in promoting epithelial wound healing and host defense. J Biol Chem 280: 15267-15278.

198. Devchand PR, Schmidt BA, Primo VC, Zhang QY, Arnaout MA, et al. (2005) A synthetic eicosanoid LX-mimetic unravels host-donor interactions in allogeneic BMT-induced GvHD to reveal an early protective role for host neutrophils. FASEB J 19: 203-210.

199. Papayianni A, Serhan CN, Phillips ML, Rennke HG, Brady HR (1995) Transcellular biosynthesis of lipoxin A4 during adhesion of platelets and neutrophils in experimental immune complex glomerulonephritis 47: 1295-1302.

200. Svensson CI, Zattoni M, Serhan CN (2007) Lipoxins and aspirin-triggered lipoxin inhibit inflammatory pain processing. J Exp Med 204: 245-252.

201. Abdelmoaty S, Wigerblad G, Bas DB, Codeluppi S, Fernandez-Zafra T, 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. 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.

203. 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. Prostaglandins Leukot Essent Fatty Acids 84: 43-50.

204. Conte FP, Menezes-de-Lima O Jr, Verri WA Jr, Cunha FQ, Penido C, et al. (2010) Lipoxin A(4) attenuates zymosan-induced arthritis by modulating endothelin-1 and its effects. Br J Pharmacol 161: 911-924.

205. Zhou M, Chen B, Sun H, Deng Z, Andersson R, et al. (2011) The protective effects of Lipoxin A4 during the early phase of severe acute pancreatitis in rats. Scand J Gastroenterol 46: 211-219.

206. Tobin 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.

207. Walker J, Dichter E, 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.

208. Shryock N, McBerry C, Salazar Gonzalez RM, Janes S, Costa FT, et al. (2013) Lipoxin Aâ„ and 15-epi-lipoxin Aâ„ protect against experimental cerebral malaria by inhibiting IL-12/IFN-Î³ in the brain. PLoS One 8: e61882.

209. Molina-Berríos A, Campos-Estrada C, Henriquez N, Faúndez M, Torres G, et al. (2013) Protective role of acetylsalicylic acid in experimental Trypanosoma cruzi infection: evidence of a 15-epi-lipoxin Aâ„-mediated effect. PLoS Negl Trop Dis 7: e2173.

210. 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. Proc Natl Acad Sci U S A 107: 14298-14303.

211. Arita M, Yoshida M, Hong S, Tjonahen 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.

212. Aoki H, Hisada T, Ishizuka T, Utsugi M, Ono A, et al. (2010) Protective effect of resolvin E1 on the development of asthmatic airway inflammation. Biochem Biophys Res Commun 400: 128-133.

213. Aoki H, Hisada T, Ishizuka T, Utsugi M, Kawata T, et al. (2008) Resolvin E1 dampens airway inflammation and hyperresponsiveness in a murine model of asthma. Biochem Biophys Res Commun 367: 509-515.

214. Xu ZZ, Zhang L, Liu T, Park JY, Berta T, et al. (2010) Resolvins RvE1 and RvD1 attenuate inflammatory pain via central and peripheral actions. Nat Med 16: 592-597, 1p following 597.

215. Xu ZZ, Berta T, Ji RR (2013) Resolvin E1 inhibits neuropathic pain and spinal cord microglial activation following peripheral nerve injury. J Neuroimmune Pharmacol 8: 37-41.

216. Rajasagi 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 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 antinociception. 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. Settimio 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: 318621.

231. Bento AF, Claudino RF, Dutra RC, Marcon R, Calixto 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, Irimia 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, Kohli 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. Lukiw WJ, Bazan NG (2008) Docosahexaenoic acid and the aging brain. J Nutr 138: 2510-2514.

237. Kenchegowda S, He J, Bazan 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.

This article was originally published in a special issue, **Aging and Immunization** handled by Editor(s). Dr. Pierre Olivier Lang, Medical school and University hospitals of Geneva, Switzerland