Specialized Pro-Resolving Mediators Biomarkers

Subjects: Rheumatology | Allergy | Immunology

Contributor: Jesmond Dalli

The application of precision medicine paradigm in the daily treatment of patients has been greatly hampered by the lack of robust biomarkers. Lipid mediators are central in the regulation of host immune responses during both the initiation and resolution of inflammation. Amongst lipid mediators, the specialized pro-resolving mediators (SPM) govern immune cells to promote the resolution of inflammation. These autacoids are produced via the stereoselective conversion of essential fatty acids to yield molecules that are dynamically regulated during inflammation and exert potent immunoregulatory activities. Furthermore, there is an increasing appreciation for the role that these mediators play in conveying the biological actions of several anti-inflammatory therapeutics. Identification and quantitation of these mediators has traditionally been achieved using hyphenated mass spectrometric techniques, primarily liquid-chromatography tandem mass spectrometry.

Biomarkers | Chronic Inflammatory Conditions | Anti-Inflammatory

1. Pro-Resolving Mediators as Biomarkers in Chronic Inflammatory Conditions

Amongst the key biological activities of specialized pro-resolving mediators (SPM) is their ability to limit leukocyte infiltration to the site and counter-regulate the formation of pro-inflammatory mediators [1]. Thus, there is extensive interest in establishing whether the production of these molecules is disrupted in chronic inflammatory conditions and whether the pharmacological administration of SPM may represent a useful approach for treating such conditions. Indeed, studies conducted by many groups demonstrate that SPM production becomes dysregulated in chronic inflammatory settings and that the use of these mediators or their analogues may limit disease progression and in some instanced even reverse some of the damage.

1.1. Periodontal Disease

Periodontal disease is characterized by unremitting inflammation that results in significant damage to the periodontium. Studies in experiential settings demonstrate that SPM exert potent activities in the regulation of periodontal inflammation by limiting leukocyte trafficking to the site and downregulating the production of pro-inflammatory mediators. These molecules also promote bone and tissue repair in several models of periodontal disease [2][3][4]. In recent studies found that levels of LXA_4, PD1 and MaR1 in salivary tissues of patients with periodontal inflammation were correlated with disease severity. Intriguingly, while LXA_4 levels were observed to be negatively correlated with disease severity, those of PD1 and MaR1 were positively correlated. These results

suggest that SPM biosynthetic pathways, or potentially their degradation pathways, are differentially regulated in disease settings likely as an attempt of the host immune response to counter the ongoing inflammatory processes [5].

1.2. Rheumatoid Arthritis

This condition, as with periodontal disease, is characterized by unremitting inflammation that leads to progressive tissue destruction. Both the innate and adaptive arms of the immune response are implicated in the pathogenesis of RA. Studies in pre-clinical models demonstrate that several SPM, including RvD1 [6], RvD3 [7] and MaR1 [8], regulate disease progression. In addition, MaR1 was recently found to limit nociceptive hypersensitivity linked with inflammatory arthritis [9]. In humans, Barden et al. observed that synovial RvE2 concentrations were negatively associated with pain score whereas overall plasma SPM concentrations were negatively correlated with erythrocyte sedimentation rate, a marker of disease activity [10]. Separate studies report that serum concentrations of LXA_4, RvD1 and RvE1 are significantly reduced in patients with active RA when compared with those in remission [11]. Furthermore, plasma SPM concentrations were observed to reflect synovial disease phatotype in RA patients [12]. This observation is of interest since synovial disease phototypes were recently observed to be linked with a differential response to disease-modifying anti-rheumatic drugs [12]. Furthermore, current approaches to stratifying patients using their pathotype are somewhat cumbersome since they involve ultrasound guided biopsies. Therefore, blood SPM concentrations might provide a useful alternative for patient stratification.

1.3. Vascular Disease

Atherosclerosis is characterized by the systemic activation of immune cells that are then recruited into the vascular wall and contribute to the accumulation of lipids. Studies in experimental systems demonstrate that loss of ALOX15, a key enzyme in SPM production, was linked with increased vascular lipid load in atherosclerosis prone mice [13]. Pharmacological studies demonstrate that SPM regulate various aspects of disease development. Whereby, 15-epi-LXA_4 and RvE1 were observed to limit the migration of human saphenous vein SMCs and decrease phosphorylation of the platelet-derived growth factor receptor-β [14]. RvD1 was also observed to exert protective activities in regulating atheroprogression by improving the uptake of apoptotic cells within atherosclerotic lesions, reducing lesional oxidative stress and increasing the thickness of the fibrous cap. RvD2 and MaR1 regulate disease progression in experimental settings this time by reducing macrophage accumulation in vascular tissues and increasing the number of smooth muscle cells [15]. By contrast, $RvD5_{n\text{-}3\ DPA}$ decreased disease progression by limiting platelet leukocyte interactions [16].

SPM levels are also observed to be altered in humans where the concentrations of RvD1 are markedly reduced in vulnerable regions from human carotid atherosclerotic plaques [17]. Plasma levels of 15-epi-LXA_4 are significantly lower in patients with symptomatic peripheral artery disease than in healthy volunteers [14]. Similarly, peripheral blood n-3 DPA-derived resolvin ($RvD_{n\text{-}3\ DPA}$) concentrations are lower in patients with cardiovascular disease when compared with those observed in healthy volunteers [16]. This reduction in $RvD_{n\text{-}3\ DPA}$ concentrations is linked with

an increased activation of circulating phagocytes [16], suggesting that these molecules might be useful indicators of vascular disease.

1.4. Allergic Inflammation

The biological activities of SPM are also described in allergic conditions including allergic airway diseases such as asthma and allergic rhinitis. In recent studies, RvE3 was observed to reduce the total numbers of inflammatory cells and eosinophils recruited into the lung of mice sensitized and challenged with house dust mite. This mediator also reduced the levels of IL-23 and IL-17 in lavage fluid and suppressed the expression of IL-23 and IL-17A mRNA expression in lung and peribronchial lymph node. Importantly, these cellular and molecular changes were linked with a reduction in lung resistance in mice treated with RvE3 [18]. In a murine model of allergic asthma, RvE1 promoted a decrease in leukocyte recruitment into the lung and downregulated the expression of pro-inflammatory cytokines in lavage fluids and in macrophages [19]. In separate studies, the DHA-derived RvD1 and AT-RvD1 were observed to exert protective activities in murine models of asthma. Here, RvD1 markedly decreased airway eosinophilia and mucus metaplasia and downregulated the expression of IL-5 and IκBα degradation. AT-RvD1 also regulated lung inflammation in these settings, leading to a marked decrease in the resolution interval for lung eosinophilia and the expression of inflammatory peptide and lipid mediators, actions that together contributed to an accelerated resolution of airway hyperreactivity to methacholine [20].

The protective activities of SPM are also observed with phagocytes from patients with asthma whereby AT-RvD1 reduced TNF-α levels in peripheral blood mononuclear cells from patients with severe asthma stimulated with lipopolysaccharide or *Dermatophagoides pteronyssinus*. This SPM also increased phagocytosis of apoptotic neutrophils by monocytes from patients with severe asthma [21]. PD1 was recently observed to display protective activities in regulating eosinophil biology, a key cell type linked with the propagation of allergic inflammation. Indeed, this SPM limited chemotaxis of these cells towards CCL11/eotaxin-1 and 5-oxo-eicosatetraenoic acid. PD1 also modulated the expression of the adhesion molecules CD11b and L-selectin on these cells [22].

1.5. COVID-19

The potent bioactions of SPM in regulating both innate and adaptive immune responses, together with a mounting body of evidence suggesting that the production of these mediators may be dysregulated in hospitalized patients with COVID-19, have sparked interest in evaluating whether these molecules could provide novel leads in treating the excessive inflammatory response observed in these patients. While the direct evidence on the therapeutic potential of these molecules in COVID-19 is at present limited, studied performed thus far in these patients, as well as in other respiratory viral infections such as H1N1, are encouraging. Indeed, in recent studies the incubation of phagocytes from COVID-19 with SPM rectifies their abilities to uptake and kill bacteria. These mediators also downregulate the expression of activation markers on circulating phagocytes, including tissue factor (CD142), which was recently linked with an increased risk of thrombosis in these patients [23]. Furthermore, RvD2, RvD3, MCTR3 and PCTR3 downregulated the expression of inflammatory cytokines in monocyte-derived macrophages from patients with COVID-19, including IFNγ and TNF-α [24]. In murine studies with influenza infections, the

protectin family of mediators was observed to both regulate the inflammatory response and limit viral replication by inhibiting the viral export machinery [25]. By contrast, the D-series resolving precursor 17-HDHA increased antigen-specific Ab titers to pH1N1 virus. 17-HDHA also increased the number of antigen-specific antigen-secreting cells present in the bone marrow. Intriguingly, the 17-HDHA-mediated-increased antigen production was more protective against live pH1N1 influenza infection in mice [26]. Together, these findings suggest that SPM may hold promise as new therapeutics for COVID-19 by reprogramming both the innate and adaptive arms of the immune response to decrease inflammation and enhance anti-viral immunity.

2. SPM as Biomarkers for Determining Therapeutic Efficacy of Anti-Inflammatory Drugs

Studies investigating the mechanisms of action of several widely used therapeutics such as statins and aspirin suggest a role for SPM in mediating their anti-inflammatory activities. For example, aspirin, in addition to inhibiting prostaglandin and thromboxane formation, promotes the formation epimeric forms of the resolvins, protectins and lipoxins via the acetylation of COX-2 [27][28]. Indeed, this reaction ablates the ability of the enzyme to catalyze the formation of PGG_2 while retaining its ability to oxygenate AA on carbon 15 and DHA on carbon 17. These mediators display similar binding affinities to the cognate receptor for the ALOX-derived molecules while displaying enhanced stability to metabolic inactivation [29]. The ability of aspirin, in particular low dose aspirin, to upregulate the formation of these molecules was also established in humans, whereby Chiang and colleagues demonstrated in a randomized trial that low dose aspirin, at variance to high dose aspirin, upregulated plasma 15-epi-LXA_4 (also referred to as AT-LXA_4) concentrations [30]. Intriguingly, the ability of aspirin to increase 15-epi-LXA_4 concentrations in healthy volunteers was observed to be dependent on gender and age. Where, a positive correlation was observed in females with age, whilst a negative correlation was found in males in the ability of aspirin to increase plasma 15-epi-LXA_4 [31]. The gender-specific differences in AT-SPM regulation appear to be tissue or potentially condition-specific. In a separate study, the regulation of 15-epi-LXA_4 by aspirin in gingival crevicular fluid of patients with periodontal disease was not observed to be different between males and females [32]. These findings suggest that while aspirin may regulate the formation of AT-SPM in distinct tissues; factors such as age, gender and disease may have an influence on the individual mediators being regulated (i.e., 15-epi-LXA_4 vs. 17R-RvD1 vs. 17R-PD1) and the direction of change (i.e., upregulated or downregulated). Thus, future studies will need to establish which of these autacoids is diagnostic of aspirin efficacy in specific patient populations and target tissue or fluid (e.g., plasma).

Another class of drugs that regulates SPM formation is the statins. In experimental lung inflammation, Lovastatin increases 15-epi-LXA_4 concentrations via the upregulation of 14,15-epoxyeicosatrienoic acid by airway epithelial cells [33]. Atorvastatin was observed to also upregulate 15-epi-LXA_4 levels in the heart, albeit via a different mechanism to that observed in the lung. Indeed, atorvastatin regulates cyclooxygenase-2 and 5-lipoxygenase activity to increase 15-epi-LXA_4 levels [34]. In vascular endothelial cells, atorvastatin also regulates COX-2 activity by promoting nitrosylation of the enzyme, a reaction that was dependent on the activity of the nitric oxide synthase [35]. This mechanism contributed to the upregulation of 13-series resolvins (RvT) that display potent immune

regulatory activity on phagocytes. Indeed, pharmacological inhibition of COX-2 activity blocked RvT formation and reversed the protective activities of atorvastatin in both experimental joint inflammation and bacterial infections [35][36].

Recent studies suggest that dexamethasone may also upregulate SPM formation [37]. In experimental allergic inflammation levels of the DHA-derived protectins and those of resolvin pathway marker 17-HDHA were increased by this corticosteroid. This regulation of SPM levels by this potent anti-inflammatory drug was retained in human airway inflammation, with levels of several SPM, including the DHA-derived PD1 and the n-3 DPA-derived $MaR1_{n-3\ DPA}$, being markedly upregulated in plasma of patients with COVID-19 treated with dexamethasone [24]. Intriguingly, these observations were linked with the upregulation of several SPM biosynthetic enzymes in circulating leukocytes from patients treated with dexamethasone [24]. These observations suggest that dexamethasone increases SPM formation by regulating the expression of their biosynthetic enzymes.

3. Potential for the Use of SPM as Biomarkers for Determining the Utility of Omega-3 Supplements in Regulating Inflammation

Omega-3 supplements have long been held to exert beneficial actions in the regulation of inflammation with a plethora of studies in experimental systems supporting their utility in a range of inflammatory conditions, including cardiovascular disease and arthritis [38][39][40]. The evidence in humans has been less clear-cut, with studies observing both beneficial and potentially harmful effects or no effects. One should note that studies in humans have used a wide range of doses as well as forms of these fatty acids and the influence of these variables on their bioavailability, amongst others, are not fully understood. Given that omega-3 fatty acids are substrates in the formation of SPM, several groups have investigated whether the beneficial actions of these supplements are at least in part linked with the upregulation of these protective autacoids. Studies conducted in humans appear to support this hypothesis. In patients with minor cognitive impairment, the administration of an omega-3 supplement increased plasma RvD1 concentrations and improved cognitive function in these patients [41]. Of note, the epimeric form of RvD1, 17R-RvD1, which exerts its biological actions via the same receptors, was previously reported to also limit post-operative cognitive decline in an experimental model of surgical-induced cognitive decline [42]. In patients with chronic kidney disease, supplementation with omega-3 fatty acids led to an increased production of SPM, primarily RvE1, RvE2, RvE3 and RvD5, by isolated peripheral blood neutrophils. This increase in SPM production was linked with a decrease in myeloperoxidase levels, a marker of neutrophil activation, in plasma from patients receiving omega-3 fatty acids [43].

Recent studies have also started to address the pharmacokinetics of omega-3 supplements by using SPM as functional biomarkers. In studies performed in healthy volunteers, plasma SPM concentrations reached a maximum as early as 2 h after the oral ingestion of the supplement [44]. This increase was also dependent on the initial dose of omega-3 supplement provided, establishing a link between substrate availability and conversion to SPM. Furthermore, in these studies plasma levels of several SPM were correlated with changes in both peripheral blood phagocyte and platelet activation. Of note, plasma levels of these autacoids also rapidly decreased in

peripheral blood of healthy volunteers given a single dose of omega-3 supplement, returning to baseline values between 2–24 h after supplementation depending on the supplement dose administered. This observation is in line with the biology of SPM, whereby, as autacoids, these molecules are further metabolized and cleared from the tissue. Experimental evidence obtained so far on the kinetics of these processes has primarily focused on in vitro systems, demonstrating that the rates of conversion of these autacoids varies between different molecules [29][45][46]. Furthermore, some of the further metabolites described for these molecules retain the biological activities of the parent molecule [29][45][46]. These aspects will need to be taken into consideration when devising strategies to monitor supplement efficacy in patient populations.

Notably, in instances where supplements are administered over longer periods to those employed, there may be some flexibility regarding the timing employed between supplementation and sample collection. These patients were administered the supplement for 7 days and then blood was collected. Here, plasma SPM levels of these autacoids were elevated several hours after the administration of the last supplement dose compared to pre-supplement levels. These findings suggest that chronic administration may result in sustained substrate release, likely from esterified pools that can support SPM formation for longer periods to those achieved with a single equivalent supplement dose. Furthermore, plasma SPM concentrations in patients with periphery artery disease were increased in dose-dependent manner, an increase that was linked with changes in peripheral blood phagocytes response [47]. Together these observations lend support to the potential utility of peripheral blood SPM as functional biomarkers in determining the efficacy of supplementation at regulating inflammation.

References

1. Serhan, C.N.; Levy, B.D. Resolvins in inflammation: Emergence of the pro-resolving superfamily of mediators. J. Clin. Investig. 2018, 128, 2657–2669.
2. Maekawa, T.; Hosur, K.; Abe, T.; Kantarci, A.; Ziogas, A.; Wang, B.; Van Dyke, T.E.; Chavakis, T.; Hajishengallis, G. Antagonistic effects of IL-17 and D-resolvins on endothelial Del-1 expression through a GSK-3beta-C/EBPbeta pathway. Nat. Commun. 2015, 6, 8272.
3. Freire, M.O.; Dalli, J.; Serhan, C.N.; Van Dyke, T.E. Neutrophil Resolvin E1 Receptor Expression and Function in Type 2 Diabetes. J. Immunol. 2017, 198, 718–728.
4. Wang, C.W.; Colas, R.A.; Dalli, J.; Arnardottir, H.H.; Nguyen, D.; Hasturk, H.; Chiang, N.; Van Dyke, T.E.; Serhan, C.N. Maresin 1 Biosynthesis and Proresolving Anti-infective Functions with Human-Localized Aggressive Periodontitis Leukocytes. Infect. Immun. 2015, 84, 658–665.
5. Tobon-Arroyave, S.I.; Isaza-Guzman, D.M.; Gomez-Ortega, J.; Florez-Alzate, A.A. Salivary levels of specialized pro-resolving lipid mediators as indicators of periodontal health/disease status. J. Clin. Periodontol. 2019, 46, 978–990.
6. Norling, L.V.; Headland, S.E.; Dalli, J.; Arnardottir, H.H.; Haworth, O.; Jones, H.R.; Irimia, D.; Serhan, C.N.; Perretti, M. Proresolving and cartilage-protective actions of resolvin D1 in

inflammatory arthritis. JCI Insight 2016, 1, e85922.

7. Arnardottir, H.H.; Dalli, J.; Norling, L.V.; Colas, R.A.; Perretti, M.; Serhan, C.N. Resolvin D3 Is Dysregulated in Arthritis and Reduces Arthritic Inflammation. J. Immunol. 2016, 197, 2362–2368.
8. Jin, S.; Chen, H.; Li, Y.; Zhong, H.; Sun, W.; Wang, J.; Zhang, T.; Ma, J.; Yan, S.; Zhang, J.; et al. Maresin 1 improves the Treg/Th17 imbalance in rheumatoid arthritis through miR-21. Ann. Rheum. Dis. 2018, 77, 1644–1652.
9. Allen, B.L.; Montague-Cardoso, K.; Simeoli, R.; Colas, R.A.; Oggero, S.; Vilar, B.; McNaughton, P.A.; Dalli, J.; Perretti, M.; Sher, E.; et al. Imbalance of proresolving lipid mediators in persistent allodynia dissociated from signs of clinical arthritis. Pain 2020, 161, 2155–2166.
10. Barden, A.E.; Moghaddami, M.; Mas, E.; Phillips, M.; Cleland, L.G.; Mori, T.A. Specialised pro-resolving mediators of inflammation in inflammatory arthritis. Prostaglandins Leukot. Essent. Fatty Acids 2016, 107, 24–29.
11. Ozgul Ozdemir, R.B.; Soysal Gunduz, O.; Ozdemir, A.T.; Akgul, O. Low levels of pro-resolving lipid mediators lipoxin-A4, resolvin-D1 and resolvin-E1 in patients with rheumatoid arthritis. Immunol. Lett. 2020, 227, 34–40.
12. Gomez, E.A.; Colas, R.A.; Souza, P.R.; Hands, R.; Lewis, M.J.; Bessant, C.; Pitzalis, C.; Dalli, J. Blood pro-resolving mediators are linked with synovial pathology and are predictive of DMARD responsiveness in rheumatoid arthritis. Nat. Commun. 2020, 11, 5420.
13. Merched, A.J.; Ko, K.; Gotlinger, K.H.; Serhan, C.N.; Chan, L. Atherosclerosis: Evidence for impairment of resolution of vascular inflammation governed by specific lipid mediators. FASEB J. 2008, 22, 3595–3606.
14. Ho, K.J.; Spite, M.; Owens, C.D.; Lancero, H.; Kroemer, A.H.; Pande, R.; Creager, M.A.; Serhan, C.N.; Conte, M.S. Aspirin-triggered lipoxin and resolvin E1 modulate vascular smooth muscle phenotype and correlate with peripheral atherosclerosis. Am. J. Pathol. 2010, 177, 2116–2123.
15. Viola, J.R.; Lemnitzer, P.; Jansen, Y.; Csaba, G.; Winter, C.; Neideck, C.; Silvestre-Roig, C.; Dittmar, G.; Doring, Y.; Drechsler, M.; et al. Resolving Lipid Mediators Maresin 1 and Resolvin D2 Prevent Atheroprogression in Mice. Circ. Res. 2016, 119, 1030–1038.
16. Colas, R.A.; Souza, P.R.; Walker, M.E.; Burton, M.; Zaslona, Z.; Curtis, A.M.; Marques, R.M.; Dalli, J. Impaired Production and Diurnal Regulation of Vascular RvDn-3 DPA Increase Systemic Inflammation and Cardiovascular Disease. Circ. Res. 2018, 122, 855–863.
17. Fredman, G.; Hellmann, J.; Proto, J.D.; Kuriakose, G.; Colas, R.A.; Dorweiler, B.; Connolly, E.S.; Solomon, R.; Jones, D.M.; Heyer, E.J.; et al. An imbalance between specialized pro-resolving lipid mediators and pro-inflammatory leukotrienes promotes instability of atherosclerotic plaques. Nat. Commun. 2016, 7, 12859.

18. Sato, M.; Aoki-Saito, H.; Fukuda, H.; Ikeda, H.; Koga, Y.; Yatomi, M.; Tsurumaki, H.; Maeno, T.; Saito, T.; Nakakura, T.; et al. Resolvin E3 attenuates allergic airway inflammation via the interleukin-23-interleukin-17A pathway. FASEB J. 2019, 33, 12750–12759.
19. Flesher, R.P.; Herbert, C.; Kumar, R.K. Resolvin E1 promotes resolution of inflammation in a mouse model of an acute exacerbation of allergic asthma. Clin. Sci. 2014, 126, 805–814.
20. Rogerio, A.P.; Haworth, O.; Croze, R.; Oh, S.F.; Uddin, M.; Carlo, T.; Pfeffer, M.A.; Priluck, R.; Serhan, C.N.; Levy, B.D. Resolvin D1 and aspirin-triggered resolvin D1 promote resolution of allergic airways responses. J. Immunol. 2012, 189, 1983–1991.
21. Zambalde, E.P.; Teixeira, M.M.; Favarin, D.C.; de Oliveira, J.R.; Magalhaes, M.L.; Cunha, M.M.; Silva, W.C.J.; Okuma, C.H.; Rodrigues, V.J.; Levy, B.D.; et al. The anti-inflammatory and pro-resolution effects of aspirin-triggered RvD1 (AT-RvD1) on peripheral blood mononuclear cells from patients with severe asthma. Int. Immunopharmacol. 2016, 35, 142–148.
22. Miyata, J.; Fukunaga, K.; Iwamoto, R.; Isobe, Y.; Niimi, K.; Takamiya, R.; Takihara, T.; Tomomatsu, K.; Suzuki, Y.; Oguma, T.; et al. Dysregulated synthesis of protectin D1 in eosinophils from patients with severe asthma. J. Allergy Clin. Immunol. 2013, 131, 353–360.
23. Hottz, E.D.; Azevedo-Quintanilha, I.G.; Palhinha, L.; Teixeiraet, L.; Barreto, E.A.; Pão, C.R.R.; Righy, C.; Franco, S.; Souza, T.M.L.; Kurtz, P.; et al. Platelet activation and platelet-monocyte aggregate formation trigger tissue factor expression in patients with severe COVID-19. Blood 2020, 136, 1330–1341.
24. Koenis, D.S.; Beegun, I.; Jouvene, C.C.; Aguirre, G.A.; Souza, P.R.; Gonzalez-Nunez, M.; Ly, L.; Pistorius, K.; Kocher, H.M.; Ricketts, W.; et al. Disrupted Resolution Mechanisms Favor Altered Phagocyte Responses in COVID-19. Circ. Res. 2021, 129, e54–e71.
25. Morita, M.; Kuba, K.; Ichikawa, A.; Nakayama, M.; Katahira, J.; Iwamoto, R.; Watanebe, T.; Sakabe, S.; Daidoji, T.; Nakamura, S.; et al. The lipid mediator protectin D1 inhibits influenza virus replication and improves severe influenza. Cell 2013, 153, 112–125.
26. Ramon, S.; Baker, S.F.; Sahler, J.M.; Kim, N.; Feldsott, E.A.; Serhan, C.N.; Martinez-Sobrido, L.; Topham, D.J.; Phipps, R.P. The specialized proresolving mediator 17-HDHA enhances the antibody-mediated immune response against influenza virus: A new class of adjuvant? J. Immunol. 2014, 193, 6031–6040.
27. Serhan, C.N.; Hong, S.; Gronert, K.; Colgan, S.P.; Devchand, P.R.; Mirick, G.; Moussignac, R.L. Resolvins: A family of bioactive products of omega-3 fatty acid transformation circuits initiated by aspirin treatment that counter proinflammation signals. J. Exp. Med. 2002, 196, 1025–1037.
28. Claria, J.; Serhan, C.N. Aspirin triggers previously undescribed bioactive eicosanoids by human endothelial cell-leukocyte interactions. Proc. Natl. Acad. Sci. USA 1995, 92, 9475–9479.

29. Sun, Y.P.; Oh, S.F.; Uddin, J.; Yang, R.; Gotlinger, K.; Campbell, E.; Colgan, S.P.; Petasis, N.A.; Serhan, C.N. Resolvin D1 and its aspirin-triggered 17R epimer. Stereochemical assignments, anti-inflammatory properties, and enzymatic inactivation. J. Biol. Chem. 2007, 282, 9323–9334.
30. Chiang, N.; Bermudez, E.A.; Ridker, P.M.; Hurwitz, S.; Serhan, C.N. Aspirin triggers antiinflammatory 15-epi-lipoxin A4 and inhibits thromboxane in a randomized human trial. Proc. Natl. Acad. Sci. USA 2004, 101, 15178–15183.
31. Chiang, N.; Hurwitz, S.; Ridker, P.M.; Serhan, C.N. Aspirin has a gender-dependent impact on antiinflammatory 15-epi-lipoxin A4 formation: A randomized human trial. Arterioscler. Thromb. Vasc. Biol. 2006, 26, e14–e17.
32. Bali, S.K.; Madaiah, H.; Dharmapalan, J.; Janarthanam, S.; Tarannum, F. Effect of systemic long-term, low-dose aspirin on periodontal status and soluble CD14 in gingival crevicular fluid: A case-control study. J. Investig. Clin. Dent. 2018, 9, e12353.
33. Planaguma, A.; Pfeffer, M.A.; Rubin, G.; Croze, R.; Uddin, M.; Serhan, C.N.; Levy, B.D. Lovastatin decreases acute mucosal inflammation via 15-epi-lipoxin A4. Mucosal. Immunol. 2010, 3, 270–279.
34. Birnbaum, Y.; Ye, Y.; Lin, Y.; Freeberg, S.Y.; Nishi, S.P.; Martinez, J.D.; Huang, M.H.; Uretsky, B.F.; Perez-Polo, J.R. Augmentation of myocardial production of 15-epi-lipoxin-a4 by pioglitazone and atorvastatin in the rat. Circulation 2006, 114, 929–935.
35. Dalli, J.; Chiang, N.; Serhan, C.N. Elucidation of novel 13-series resolvins that increase with atorvastatin and clear infections. Nat. Med. 2015, 21, 1071–1075.
36. Walker, M.E.; Souza, P.R.; Colas, R.A.; Dalli, J. 13-Series resolvins mediate the leukocyte-platelet actions of atorvastatin and pravastatin in inflammatory arthritis. FASEB J. 2017, 31, 3636–3648.
37. Pyrillou, K.; Chairakaki, A.D.; Tamvakopoulos, C.; Andreakos, E. Dexamethasone induces omega3-derived immunoresolvents driving resolution of allergic airway inflammation. J. Allergy Clin. Immunol. 2018, 142, 691–695.
38. Carracedo, M.; Artiach, G.; Arnardottir, H.; Back, M. The resolution of inflammation through omega-3 fatty acids in atherosclerosis, intimal hyperplasia, and vascular calcification. Semin. Immunopathol. 2019, 41, 757–766.
39. Abdulrazaq, M.; Innes, J.K.; Calder, P.C. Effect of omega-3 polyunsaturated fatty acids on arthritic pain: A systematic review. Nutrition 2017, 39, 57–66.
40. Yates, C.M.; Calder, P.C.; Ed Rainger, G. Pharmacology and therapeutics of omega-3 polyunsaturated fatty acids in chronic inflammatory disease. Pharmacol. Ther. 2014, 141, 272–282.

41. Fiala, M.; Halder, R.C.; Sagong, B.; Ross, O.; Sayre, J.; Porter, V.; Bredesen, D.E. omega-3 Supplementation increases amyloid-beta phagocytosis and resolvin D1 in patients with minor cognitive impairment. FASEB J. 2015, 29, 2681–2689.
42. Terrando, N.; Gomez-Galan, M.; Yang, T.; Carlstrom, M.; Gustavsson, D.; Harding, R.E.; Lindskog, M.; Eriksson, L.I. Aspirin-triggered resolvin D1 prevents surgery-induced cognitive decline. FASEB J. 2013, 27, 3564–3571.
43. Barden, A.E.; Shinde, S.; Burke, V.; Puddey, I.B.; Beilin, L.J.; Irish, A.B.; Watts, G.F.; Mori, T.A. The effect of n-3 fatty acids and coenzyme Q10 supplementation on neutrophil leukotrienes, mediators of inflammation resolution and myeloperoxidase in chronic kidney disease. Prostaglandins Other Lipid Mediat. 2018, 136, 1–8.
44. Souza, P.R.; Marques, R.M.; Gomez, E.A.; Colas, R.A.; De Matteis, R.; Zak, A.; Patel, M.; Collier, D.J.; Dalli, J. Enriched Marine Oil Supplements Increase Peripheral Blood Specialized Pro-Resolving Mediators Concentrations and Reprogram Host Immune Responses: A Randomized Double-Blind Placebo-Controlled Study. Circ. Res. 2020, 126, 75–90.
45. Claria, J.; Dalli, J.; Yacoubian, S.; Gao, F.; Serhan, C.N. Resolvin D1 and resolvin D2 govern local inflammatory tone in obese fat. J. Immunol. 2012, 189, 2597–2605.
46. Colas, R.A.; Dalli, J.; Chiang, N.; Vlasakov, I.; Sanger, J.M.; Riley, I.R.; Serhan, C.N. Identification and Actions of the Maresin 1 Metabolome in Infectious Inflammation. J. Immunol. 2016, 197, 4444–4452.
47. Schaller, M.S.; Chen, M.; Colas, R.A.; Sorrentino, T.A.; Lazar, A.A.; Grenon, S.M.; Dalli, J.; Conte, M.S. Treatment With a Marine Oil Supplement Alters Lipid Mediators and Leukocyte Phenotype in Healthy Patients and Those With Peripheral Artery Disease. J. Am. Heart Assoc. 2020, 9, e016113.