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Inflammation resolution and specialized pro-resolving lipid mediators in chronic rhinosinusitis

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Abstract

Introduction: In chronic rhinosinusitis (CRS), a complex pathophysiology results from varied pro-inflammatory stimuli but is consistently characterized by classic cellular, molecular, and microbial alterations. Normally, endogenous specialized pro-resolving mediators (SPM) actively promote resolution of inflammation through numerous pathways including those involved in host antimicrobial defense. However, these pathways appear to be disrupted in CRS.

Areas covered: This paper describes features of CRS in the context of chronic tissue inflammation, and potential mechanisms by which specialized pro-resolving mediators promote active resolution of tissue inflammation.

Expert opinion: Temporal phases of resolution must be tightly regulated to successfully resolve inflammation in CRS while preserving tissue functions such as barrier maintenance and special sensory function. Dysregulation of SPM enzymatic pathways has been recently shown in CRS and is associated with disease phenotypes and microbial colonization patterns. Current research in animal models and in vitro human cell culture, as well as human dietary studies, demonstrate relevant changes in cell signaling with lipid mediator bioavailability. Further clinical research may provide insight into the therapeutic value of this approach in CRS.

Keywords

airway disease; chronic rhinosinusitis; lipoxin; LXA4; mucosal inflammation; paranasal sinus; resolving; RvD1; RvD2; Sinusitis; specialized pro-resolving mediators

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Declaration of interest

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1. Introduction

Chronic Rhinosinusitis (CRS), a disease defined by sinonasal inflammation lasting greater than three months, is characterized by nasal obstruction, drainage, facial pressure, and olfactory loss [1,2]. CRS is phenotypically classified into two major subtypes — CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) — each associated with characteristic inflammatory profiles. More recently, CRS phenotypes have been more thoroughly defined to include: fungal rhinosinusitis, infectious rhinosinusitis, eosinophilic CRS, asthma or aspirin-exacerbated respiratory disease (AERD), cystic fibrosis, pediatric CRS, CRS associated with systemic diseases, and others [3,4]. Classic CRS histologic inflammatory sequelae include mixed inflammatory infiltrate, tissue edema, basement membrane thickening, and subepithelial fibrosis [5,6]. Numerous factors are implicated in initial CRS onset, including microbial infection, immune dysregulation, sinonasal anatomy, and concurrent allergy or asthma. A special feature of CRS is sustained tissue inflammation, despite medical therapies directed at treating the underlying etiology and offering anti-inflammatory effects. Resolution of the inflammatory response requires complex temporal and spatial regulation for the epithelium to be returned to a healthy equilibrium [2,4,5]; specialized resolving mediators have now been observed to play a critical role in this process. Reducing this chronic inflammation faciliates restored function in patients with CRS including repaired mucociliary clearance, olfactory function, and trigeminal sensation [2,7]. Alterations in microbiota colonizing the sinonasal cavity have been linked to CRS, and more recently, we observed dysregulation of lipid-derived molecules known as specialized pro-resolving mediators (SPMs) with potential links to the microbiome [8]. Understanding pro-resolving activities in the natural history of airway inflammation offers a complementary, or alternative, strategy for managing this disease.

2. Goals of CRS Treatment

The clinical goal for CRS management is reducing inflammation and improving quality of life. Administration of saline lavage, corticosteroids, and surgical procedures are mainstays of medical treatment, with antibiotics and other allergy therapies (antihistamines, leukotriene modifiers, immunotherapy, biologics) when indicated. [9,10] Several recent trials have used biologics such as omalizumab, mepolizumab, and dupilumab to modulate type 2 inflammation in refractory CRS. These monoclonal antibodies target IgE, IL-5, and IL-4/IL-13, respectively. Several phase 3 trials have documented efficacy of these agents in CRS with nasal polyps for patient reported quality of life and objective nasal polyp scores [11,12,13]. These medical treatments often are used together and may act synergistically through specific anti-inflammatory effects. [14,15] Even so, disease recalcitrance or recurrence is common, even after major interventions such as surgery. Endoscopic sinus surgery (ESS) for CRS generally yields a significant quality of life improvement[16], but a significant amount of surgical failures and cases necessitates revision surgery[17]. More advanced and aggressive surgical techniques have recently emerged, such as surgical “reboot” of the nasal mucosa. This procedure requires complete removal of diseased paranasal mucosal tissue to an opportunity for fresh re-epithelization of the mucosal surface. Removal of all diseased tissue in some studies showed a decreased recurrence of nasal polyps [18] and improved quality of life [19].

Tissue remodeling reflects the severity and chronicity of inflammation, and may further exacerbate the disease. Basement membrane thickening, fibrosis, and stromal edema are associated with highly eosinophilic environments and worse surgical outcomes [20]. These associations suggest that intentional resolution of tissue inflammation may restore local immune homeostasis and integrity of the mucosal barrier. It has been postulated that the conclusion of successful CRS management should result in restoration of normal innate and adaptive immune programs such as mucociliary clearance, healthy host-microbial interactions, and balance of immune activation versus immune tolerance. Reserve epithelial basal cells are airway-specific stem cells capable of restoring normal epithelial cellular composition once relieved of inflammatory conditions, although a recent publication suggests that airway basal cells may be reprogrammed to retain some degree of sensitivity to repeated allergic stimulus [21].

3. Inflammation Phases & Returning to Homeostatic Resolution

3.1 Phases of inflammation

Inflammation, in itself, serves a necessary physiologic purpose. It is only when inflammation becomes sustained that disease occurs in CRS and other similar diseases. Correctly mounting and resolving an inflammatory response requires a complex coordination of processes that must occur through time and space to correct the triggering insult while also preserving the host tissue to carry out its proper functions. Regeneration of the epithelial structure requires the coordination of coagulation, inflammation, and tissue proliferation. Inflammation is critical in this set of choreographed processes to restore blood supply, direct tissue synthesis, and remodel healing tissues [22, 23, 24]. In particular, type II inflammation plays an essential role in resolving inflammation. This immune segment is a powerful attenuator of the generalized tissue inflammatory response. Eosinophils, basophils, and mast cells all produce the interleukins IL-4, IL-5, and IL-13, which mediate further recruitment of eosinophils and differentiate macrophages into their inflammation-resolving phenotype. Eosinophilic activity provides crucial mediators for healing such as metalloproteinases, growth factors, and cytokines that promote wound healing and tissue remodeling. Overactivity of this process can lead to fibrosis and allergic responses [23].

Inflammation is an active process instigated by epithelium-derived cytokines in response to environmental cues. Activation of toll-like receptors on the epithelium increases the production of inflammatory cytokines and chemokines that initiate the immune response of the upper airway seen in CRS. While the resolution of inflammation was initially thought of as a passive process that would naturally occur upon removal of the stimulus, it is now accepted that resolution is an active response requiring a variety of mediators and cell types. Without proper coordination of pro-inflammatory and pro-resolving processes, chronic inflammation may arise. Chronic inflammation is often viewed as a dysregulation of this active process whereby the inflammatory response may become prolonged (Figure 1). [26].

3.2 Components of Inflammation and Wound Healing

Inflammatory resolution is the active process whereby macrophages, neutrophils, platelets, mast cells, basophils, and eosinophils cooperate to provide an optimal environment for the retsurn of healthy, functional mucosa. Disruption of communication among these components prolongs the healing process, and facilitates the transition from acute inflammation to chronic inflammation. This can present histologically in CRS with basement membrane thickening and tissue fibrosis, [6] or by TGF-beta mediated remodeling leading to formation of pseudocysts and extensive stromal tissue edema as seen in CRSwNP [25,27].

Specific cellular components of this response include the actions of pro-inflammatory macrophages to debride necrotic tissue and clear pathogens to create a suitable area for the return of normal epithelium. The process of epithelial restructuring occurs soon after the integrity of the cell barrier has been broken. Cellular migration to the injured site and subsequent basal cell differentiation forms the basis for the new epithelial barrier once inflammation has been resolved. Release of growth factors from lymphocytes and macrophages instructs the proliferation of endothelial cells for neovascularization and formation of granulation tissue produced by recruited fibroblasts in the nearby extracellular matrix. Fibroblast-derived structural proteins are key in the restoration of healthy tissue, and eventually type III collagen is replaced with type I to strengthen the tissue. [22]

3.3 Temporal Nature of Inflammation and Pro-Resolving Processes

Neutrophils are among the first immune cells to arrive at a breached epithelial barrier and play a major role in orchestration of the innate response [28]. As local production of pro-inflammatory prostaglandins and leukotrienes occurs via endothelial cells and neutrophils, a phenotypic change in neutrophils results that slows their migration and increases cellular adhesion, without compromising antimicrobial activity. As prostaglandin D_2 and E_2 levels rise, they cause class switching of lipid mediators to occur. Pro-inflammatory prostaglandins and leukotriene levels then decrease while dual-acting anti-inflammatory and pro-resolving resolvins and lipoxins are produced. These pro-resolving mediators limit further neutrophil migration, and lipoxins are able to recruit monocytes without triggering their inflammatory effects. These non-inflammatory monocytes actively scavenge pro-inflammatory cytokines and phagocytize apoptotic neutrophils to prevent spillage of these inflammatory mediators beyond the intended site of action [29]. The halting of neutrophil activity signals a shift to the inflammatory resolution phase, where pro-inflammatory cells conclude their initial physiologic response, rather than triggering chronic processes or causing excessive damage to host cells and tissues.

Once the apoptotic neutrophils have been phagocytized, macrophages are directed by these pro-resolving mediators to phenotypically transform into their M2 phenotype, known for their anti-inflammatory characteristics. This phenotypic shift is key in the resolution of inflammation (Figure 1), in particular in the suppression of inflammation and stimulation of wound repair mediated by IL-10[30]. These M2-like macrophages are known to produce maresins, which aid in the coordination of inflammation resolution by limiting neutrophilic migration and enhancing macrophage phagocytosis [31]. Macrophages also

undergo this phenotypic shift when exposed to IL-4 and IL-13, which are secreted largely by eosinophils. The presence of neutrophils and eosinophils are characteristic of CRS, with cellular predominance in CRSsNP and CRSwNP, respectively. Neutrophilic presence suggests repeated exposure to acute inflammatory stimuli and/or inability to resolve an acute inflammatory response. Increased eosinophils could potentially affect the temporal regulation of inflammation, in addition to their other established detrimental effects on mucosal tissues. Eosinophils produce a large quantity of leukotrienes and prostaglandins in inflamed tissue, which can result in a cascade of further chemotaxis and inflammation [32]. This is one mechanism that causes the advanced remodeling seen in CRSwNP [23, 33], and likely contributes to the disease chronicity.

4. Roles and Mechanisms of Specialized Pro-Resolving Mediators in Chronic Rhinosinusitis

4.1 Defining specialized pro-resolving mediators (SPMS)

An imbalance in prostaglandins and leukotrienes produced via the inducible cyclooxygenase-2 (COX-2) and constitutively expressed cyclooxygenase-1 (COX-1) enzymes has long been thought to be a critical contributor to CRS. This has been postulated based on implications derived from aspirin-exacerbated respiratory disease (AERD) and studies in CRS tissues [34, 35]. When taken in the larger context of other fatty acid-derived mediators, we can recognize that eicosanoid regulation of CRS inflammation is considerably more complex. Specialized pro-resolving mediators (SPMs) are a novel class of polyunsaturated fatty acid (PUFA)-derived mediators that aid in facilitating the resolution of inflammation. These mediators consist of 4 major categories defined by their PUFA source and chemical structures--lipoxins, resolvins, maresins, and protectins [36].

Pro-resolving mediators are derived from arachidonic acid (AA) and the essential dietary lipids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are further processed to create many important regulators of inflammation including the eicosanoids and SPMs. AA is extracted from the phospholipids of host cell membranes by phospholipase A2 and is then converted to prostaglandins, leukotrienes, or lipoxins by cyclooxygenase and lipoxygenase enzymes. EPA and DHA, which are omega-3 PUFAs, are found in mucosal tissues and blood, allowing them to be converted to local or circulating resolvins, protectins, and maresins [37].

A variety of enzymes, pathways, and counterbalancing mediators facilitate temporospatial precision for orchestrating inflammatory balance (Figure 2). Mediators derived from DHA, include the D-class resolvins, protectins, and maresins and are produced via COX or LOX pathways. Mediators derived from EPA, such as E-class resolvins, undergo conversion to 18S-hydroxyeicoapentanoate (18S-HEPE) and 18R-HEPE via COX-2. These can be further reduced to create resolvins, RvE_1 and RvE_2 [38].

Lipoxins can also be produced from COX-2 acetylation via aspirin, creating aspirin-triggered LXA_4. Acetylation of COX-2 converts the enzyme to a 15-LOX-like enzyme; instead of prostaglandin synthesis, 15-LOX-like produces 15R-hydroxyeicosatetraenoate

(15R-HETE) from AA, which can then be converted to an analogue of 15-epi-LXA_4 [39]. This points to a mechanism for aspirin to reduce inflammation by blocking prostaglandin production and inducing the production of pro-resolving mediators [39, 40]. Resolvins can be produced in a similar fashion. D- and E-series resolvins can be generated by the acetylation of COX-2, via the production of 18R-hydroxyeicosapentaenoic acid (18R-HEPE) or 17R-HDHA (for E-class and D-class resolvins, respectively), which are subsequently converted into resolvins via LOX enzymes [41].

4.2 Sources of SPMs

The production of SPMs originates from our diet. Omega-3 and omega-6 polyunsaturated fatty acids (PUFAs) are essential to our diet, commonly found in marine lipids such as fish oil, and plants. These fatty acids are commonly stored in cell membranes, where they remain available for rapid synthesis of lipid mediators. Alpha-linolenic acid (ALA) and stearidonic acid are omega-3 plant-derived lipids that can be converted to DHA and EPA in mammals [42]. While these PUFAs are not pro-inflammatory, omega-6 PUFAs are precursors of arachidonic acid and its derivatives such as leukotrienes, thromboxanes, and prostaglandins, which may be pro-inflammatory in certain contexts. Dietary availability of each of these PUFAs can alter inflammatory responses mediated through synthesis of SPMs and mediators illustrated in Figure 2. [43. 44]

4.3 Enzymes

5-LOX, 12-LOX, and 15-LOX all show diverse capabilities to create resolvins, lipoxins, maresins, and protectins from DHA, EPA, and AA. Immunohistochemistry of human tissues has shown that these enzymes are expressed in multiple locations within the sinus mucosa. 5-LOX, 12-LOX, and 15-LOX are expressed in the cytoplasm of columnar cells in the nasal epithelium and 12-LOX nuclear staining is significantly increased in patients with nasal polyposis [40]. 12-LOX also is expressed in submucosal glands of CRS patients, whereas no staining is evident in controls. An increase in COX-1 and COX-2 levels in the cytoplasm was also observed in columnar epithelium as well as eosinophils in nasal polyp tissue. COX-2 is unique due to its significantly increased levels in submucosal glands within both the cytoplasm and the plasma membrane. [45, 46] 5-LOX activity also has been demonstrated in many immune cells such as mast cells, basophils, eosinophils, neutrophils, and macrophages. The presence of this enzyme in eosinophils and mast cells could be an indication of enzymatic dysregulation in allergic disease. [47]

Mechanisms by which arachidonic acid-derived lipoxins promote resolution of inflammation include: reduction of neutrophil chemotaxis in response to leukotriene B_4 and prostaglandins, increasing monocyte infiltration and vascular permeability, inhibiting production of reactive oxygen species, and stimulating clearance of apoptotic neutrophils by macrophages (Table 1). [48, 49] Lipoxin A_4 (LXA_4) and Lipoxin B_4 (LXB_4) are synthesized through two established pathways: 1) by 15-Lipoxygenase (15-LOX) and 5-Lipoxygenase (5-LOX), with 15-hydroxyeicosatetraenoic acid (15-HETE) as the intermediate or 2) using 5-LOX and 12-Lipoxygenase (12-LOX) with 5-hydroxyeicosatetraenoic acid (5-HETE) as the intermediate [50]. 15-HETE is also a stable intermediate that can be reliably assayed, and has pro-resolving capabilities similar to lipoxins [51].

D-series resolvins are derived from DHA by 15-LOX and 5-LOX. [40] Importantly, RvDs elicit phenotypic shifts in macrophages from the M1 to M2, allowing for a more permissive environment for inflammatory resolution [52]. Maresins and protectins are produced similarly to the D-series resolvins, as they are also derived from DHA via LOX enzymes. Maresins are unique in their ability to be produced by macrophages, while also being involved in the transition from the M1 to M2 macrophage phenotype and promoting regeneration of tissue. [53] Protectins have been noted for their neuroprotective activity in which they can limit neuronal injury by reducing NF-kB activity, enhancing phagocytosis, limiting leukocyte migration, and facilitating other pro-resolving functions [54].

E-series resolvins are derived from EPA. RvE_1 increases PMN apoptosis via the LTB4 receptor, inducing reactive oxygen species and activation of death domains. [55] RvE_2 activates phagocytosis and the production of anti-inflammatory cytokines. [56] RvE_3 reduces activity of PMNs at the site of inflammation. [57]

4.4 Receptors

SPMs initiate a variety of downstream pro-resolving effects through utilization of different receptors expressed in varied cell types. SPMs elicit much of their responses through G-coupled protein receptors (GPCRs) on innate immune cells. Current research indicates that E-series resolvins utilize the BLT1 and ERV1 receptors and D-Series resolvins utilize DRV/GPR32 and FPR2/ALX receptors. [58, 59] ALX is expressed by leukocytes, epithelial cells, and platelets. Its activation results in limited release of tumor necrosis factors. The DRV1/GPR32 receptor is found on epithelial cells, where receptor activation is associated with wound healing. E-series resolvins act through the ERV1/ChemR23 receptor found in leukocytes, platelets, and dendritic cells. [60] The BLT1 receptor has only been found in neutrophils. RvE1 decreases LTB4 activity by also acting through the LTB4 receptor, BLT1 [61], preventing vital signaling pathways for LTB_4 to continue the inflammatory response. Many of the SPMs uniquely bind to GPCRs, and utilize phosphorylation reactions rather than calcium signaling second messenger pathways, ultimately altering the cytoskeleton to direct cells toward pro-resolving activities. [60] In addition to independent pro-resolving activity, part of the SPM tissue response occurs through modulation or inhibition of other pro-inflammatory signaling pathways, such as the inhibition of leukotriene activity via RvE_1 and the NF-kB pathway via RvD_1.[61, 62]

5. Preclinical Studies

Studies of both human neutrophils and mouse models demonstrate that exposure to high levels of prostaglandins can increase LXA_4 production via 5-LOX. For instance, Levy et. al (2001) examined LXA_4 in relation to neutrophil activity in vitro from human pleural exudates collected from individuals with pleural effusion. The presence of LXA_4 was associated with exudates that had higher levels of neutrophils, and after administering an LXA_4 analogue to the neutrophils, PMN recruitment was halted. When an eicosanoid oxidoreductase was used to neutralize LXA_4, neutrophil infiltration was increased. Taken together, the study findings support a role for LXA_4 in limiting neutrophil taxis. [63]

Using a murine air pouch model, the same study demonstrated the role of LXA_4 in the transition from eicosanoid production to pro-resolving lipoxins, consistent with the inflammation time course described earlier in Figure 1. After injecting sterile air subcutaneously into the dorsum, mice were injected with TNF-alpha within the murine air pouch, and air pouch contents were evaluated by saline lavage. After TNF-alpha administration, there was a rapid increase in leukotrienes and PGE_2, followed by an increase in LXA_4, and ultimately neutrophil PGE_2 decrease. Use of genetically modified mice overexpressing the leukocyte LTB_4 receptor showed increased neutrophil activity and LXA_4 production in this model. To confirm the role neutrophils in LXA_4 production and self-regulation, mice were injected with neutrophil cytotoxic antibodies prior to TNF-alpha administration. Neutrophil concentrations were reduced by 30% and LXA_4 was reduced by 33%, establishing the role of neutrophils in lipoxin production These experiments demonstrate the complexity of pro-resolving mechanisms in their temporal context and inflammatory self-regulation that permits restoration of healthy tissue. Namely, LXA_4 appears to be a self-regulatory mechanism acting to limit pro-inflammatory neutrophils to prevent overly-robust or prolonged pro-inflammatory responses to tissue injury[63].

Another study assessed whether SPMs influence IgE antibody production in B cells. [64] This study isolated peripheral human B-cells and promoted differentiation to IgE production by exposure to CD40L, IL-4, and CpG oligodeoxynucleotides. IgE production was greatly decreased with exposures to RvD_1 and the RvD precursor, 17-hydroxydocosahexaenoic acid (17-HDHA). RvD_1 decreased B-cell differentiation into IgE-producing plasma cells by interfering with a vital class-switching promoter (the epsilon germline transcript promoter region), suggesting that it can be a potent inhibitor of a key part of allergic disease while also playing a part in resolving ongoing inflammation.

Finally, Koltsida et al. reported that pattern-recognition receptors can induce production of Protectin D_1 (PD_1) and RvD_1 in human monocytes and mouse macrophages.[65] Toll-like receptor 7 (TLR-7) activation was shown to induce PD_1 and RvD_1 SPM synthesis, and Tlr7 knockout mice exhibited delayed inflammatory resolution, increased lung metaplasia, and increased mucus production. Protectins and resolvins applied to these knockouts rescued resolution of this airway inflammation, indicating that TLR7 was required to abrogate Th2-driven airway inflammatory response via SPM production.

6. Potential Clinical Usage

Given its relative novelty in understanding tissue inflammation, and specialized needs for metabolite assays, few clinical studies in CRS or airway disease are currently published (Table 2). One cross-sectional study evaluated expression of leukotrienes, prostaglandins, LXA, 5-LOX, and 15-LOX concentrations in the sinonasal tissue of CRS patients. 15-LOX activity was increased in CRS patients using a metabolomics approach to study ethmoid and maxillary sinus tissue. Not surprisingly, increased levels of 15-LOX activity were observed in CRSwNP patients compared to CRSsNP [34]. Aspirin-sensitive CRSwNP patients showed decreased 15-LOX activity and increased levels of leukotrienes when compared to aspirin-tolerant CRSwNP patients. Aspirin-sensitive patients also showed

increased molecular markers of type 2 inflammation compared to aspirin-tolerant CRSwNP, as measured by IL-5.

Dysregulation of these enzymes is corroborated by a genomics study that identified a missense mutation of ALOX15, the gene responsible for encoding 15-LOX, which correlates with much lower prevalence of nasal polyposis and CRS. Mutation of the ALOX15 active site resulted in decreased activity of 15-LOX, protecting from development of CRSwNP [66]. Although other mutations found in genome-wide association studies have been associated with CRS risk, the ALOX15 mutation is arguably of greatest statistical significance and effect, supporting the importance for these lipid mediator pathways in tissue inflammation.[67]

Lipid mediators—mostly eicosanoids—have long been thought to have some physiological importance in an imbalanced inflammatory response. This imbalance has been historically approached from the increased pro-inflammatory side, but could also result from a loss of the anti-inflammatory and pro-resolving processes (Figure 3). Recently shown in lower airway diseases [68, 69, 70], a recent publication described this imbalance in patients with CRS, particularly those with nasal polyps. [8] Dysregulation of PUFA metabolism likely contributes to chronic upper airway diseases exhibiting type 2 inflammatory signatures, such as eosinophilic CRS, CRSwNP, and aspirin-exacerbated respiratory disease (AERD). These disorders exhibit similar LOX and COX dysregulation, disrupting the balance between pro-inflammatory and pro-resolving inflammatory mediators, leaving inflammation unresolved and thereby facilitating disease chronicity. In addition to pro-inflammatory eicosanoids, there is decreased production of LXA_4, possibly due to imbalance in 5- and 15-LOX activity [71]. In fact, clinical efficacy of 5-LOX inhibition in CRSwNP may be partially due to a switch from LT biosynthesis to generation of SPMs, as suggested by basic science work on the topic [72, 73].

Several studies have implicated lipid mediators in modulation of anti-microbial mucosal activities. [74, 75] To uncover interrelationships between sinonasal lipid mediators (including SPMs) and resident microbiota, one recent study profiled bacterial communities in CRS and non-CRS subjects, via ribosomal RNA gene sequencing [8]. Microbiota were profiled from middle meatal swabs while lipidomics was performed on sinus tissue obtained at surgery. Statistically significant associations were observed between microbiota composition and lipid compounds, especially 15-LOX metabolites. Dysbiosis commonly seen with CRS could negatively affect coordination needed for inflammatory resolution, and may be one obvious source of repeated or prolonged neutrophil recruitment. There have also been other recent studies documenting D-class resolvins, lipoxins, maresins, and protectins found in the surgical tissue of CRS patients. [76]

Oral supplementation of omega-3 fatty acids has been shown to increase levels of omega-3 PUFAs [42, 43, 44] and potentially decrease the burden of upper airway inflammatory disease. One study observed the effects of dietary modification in AERD, by supplementation of omega-3 PUFAs and limitation of omega-6 PUFAs.[77] After only 2 weeks of dietary modification, plasma levels of EPA and DHA metabolites increased by 2-fold and a statistically significant decrease in urinary LTE_4 and a PGD_2 metabolite

(PGD-M) were observed. Importantly, a clinical effect of this strategy to control airway mucosal inflammation was observed. The dietary intervention resulted in improved patient-reported outcomes—the 22-item Sino-Nasal Outcome Test (SNOT-22) improved by 15.1 points ($p = 0.01$) and 7-item asthma control questionnaire reduced by 0.27 points ($p = 0.03$). Another study [78] showed that with systemic corticosteroid treatment, the supplementation of omega-3 PUFAs doubled the time required for polyps to regenerate when compared to the control of exclusive corticosteroid treatment ($p < 0.0001$). These studies indicate that omega-3 PUFAs can be a strong clinical tool in the multifactorial treatment of CRS.

7. Expert Opinion

We continue to struggle with fully elucidating the etiology and pathophysiology of CRS, given the heterogeneous nature of the disease. Much of the current translational research in the field focuses on delineating phenotypes and endotypes in order to better study disease features and facilitate appropriate selection among available therapeutic options. However, the common endpoint among all classes of the disease is the transition and maintenance of the chronic inflammatory state. Existing treatments are aimed at removing possible inciting stimuli or augmenting anti-inflammatory processes using medical therapies such as saline lavage, antibiotics, corticosteroids, leukotriene modifiers, and biologic therapies, with a role for surgical correction in unresponsive disease.

A relatively simple approach to understanding CRS has proliferated in the field from early insights into disease physiology, wherein an imbalance pro-inflammatory and anti-inflammatory mechanisms is the primary problem resulting in disease, whether the factors involved are exogenous (e.g., aeroallergen) or endogenous (e.g., immune hyperresponsiveness). We must remember that inflammation is not always problematic; in fact, it is key to maintenance of tissue homeostasis. As most CRS develops in adulthood, and can result from any number or combination of stimuli, the transition from acute inflammation to sustained chronic inflammation is really the critical problem for disease development. A key concept that has been recently developed in mucosal immunology is recognition and understanding of the active endogenous process of inflammatory resolution. Incorporating this additional pillar of resolution into a temporal understanding of inflammation in mucosal homeostasis represents a new opportunity to comprehend and treat CRS. A common dictum in CRS is that it is a *chronic* disease that requires long-term maintenance therapy to keep under control. Interestingly, however, some patients do achieve disease resolution and return to tissue homeostasis.

Significant research has been done in other organ systems including the lower airway, but relatively little research into pro-resolving processes has been done to date in CRS. But the early CRS data is promising, where integration of clinical phenotyping and molecular endotyping reveals dysregulation of SPMs within CRS. With expansion of metabolomics assays and more accessible data analytics, further basic research in model systems and clinical trials promoting active resolution of inflammation through SPM modulation are expected. Dietary modification, pharmacologic intervention, or topical administration of small molecule therapies are all viable strategies to restore healthy physiology and tissue homeostasis in CRS. The regulation of these inflammatory mediators is a temporally and

spatially intricate process that must be carefully contemplated, but offers a novel approach to resolving the chronic tissue inflammation that defines CRS.

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Article highlights

- Resolution of inflammation is an active process that requires precise temporal regulation. Disruption of this process can contribute to disease chronicity
- Chronic rhinosinusitis (CRS) patients exhibit dysregulation of specialized pro-resolving mediators when compared to healthy subjects
- Specialized pro-resolving mediators are derived from omega-6 and omega-3 polyunsaturated fatty acids (PUFAs). Dietary supplementation of omega-3 PUFAs results in increased availability of precursors for these important mediators
- Not all signaling molecules are exclusively pro-inflammatory or anti-inflammatory. Molecules such as prostaglandin E2 (PGE2) have roles in both the initiation and resolution of inflammation
- One class of SPMs, resolvins, carries a significant role in allergic inflammation by reducing both IgE class switching and type II inflammation, thus limiting the eosinophilic environment commonly seen in CRS

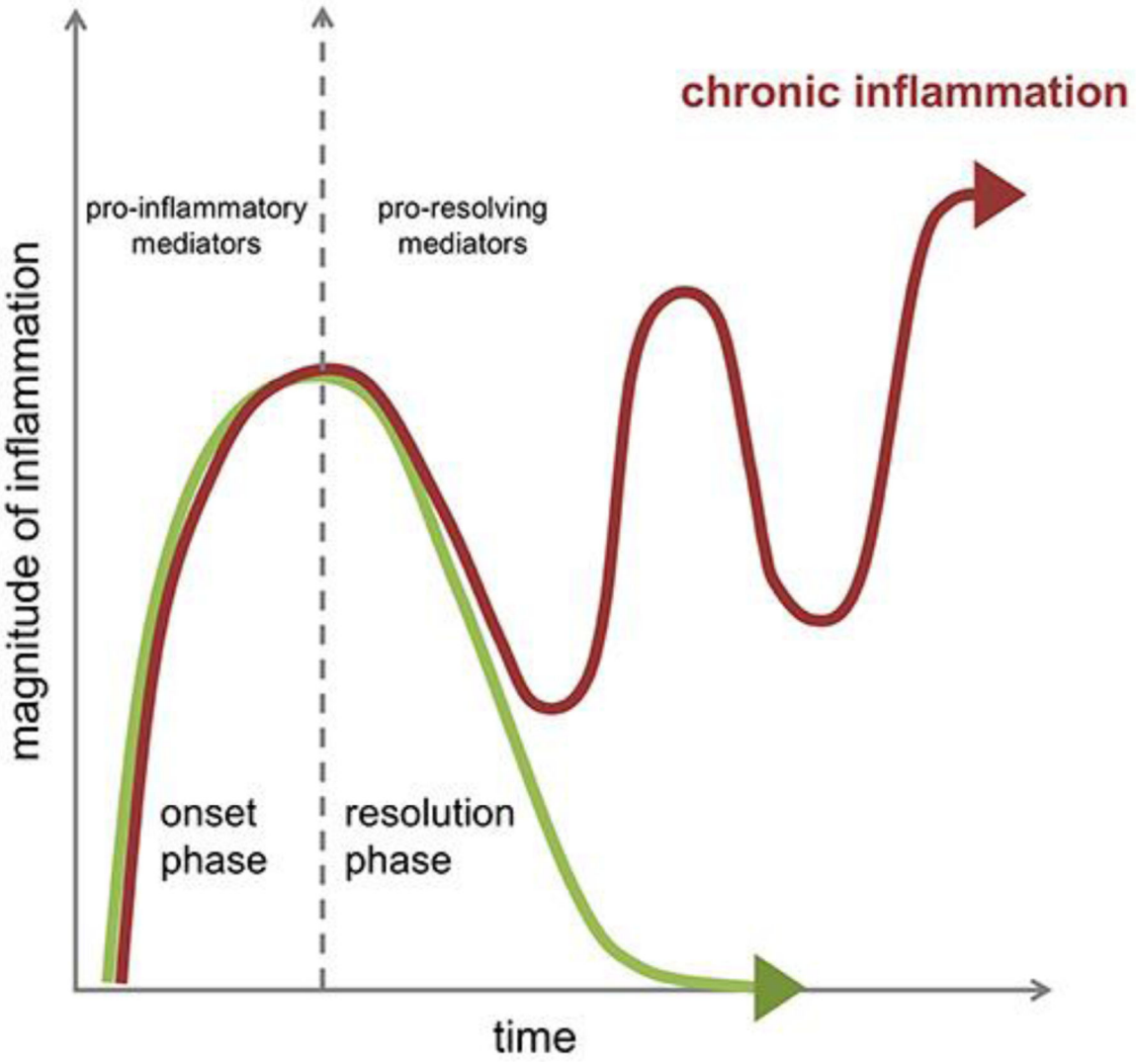

Figure 1. Phases of inflammation and resolution.

Inflammation requires an active resolution phase that is carefully coordinated. Pro-inflammatory signaling molecules such as prostaglandins and leukotrienes dominate the onset of inflammation, while pro-resolving mediators such as lipoxins and resolvins play a vital role in restoring the site of the insult back to a healthy physiological state (green timeline). The imbalance of pro-inflammatory and pro-resolving mechanisms can lead to chronic, unresolved inflammation (red timeline). *Original figure reproduced from* Ref. 79.

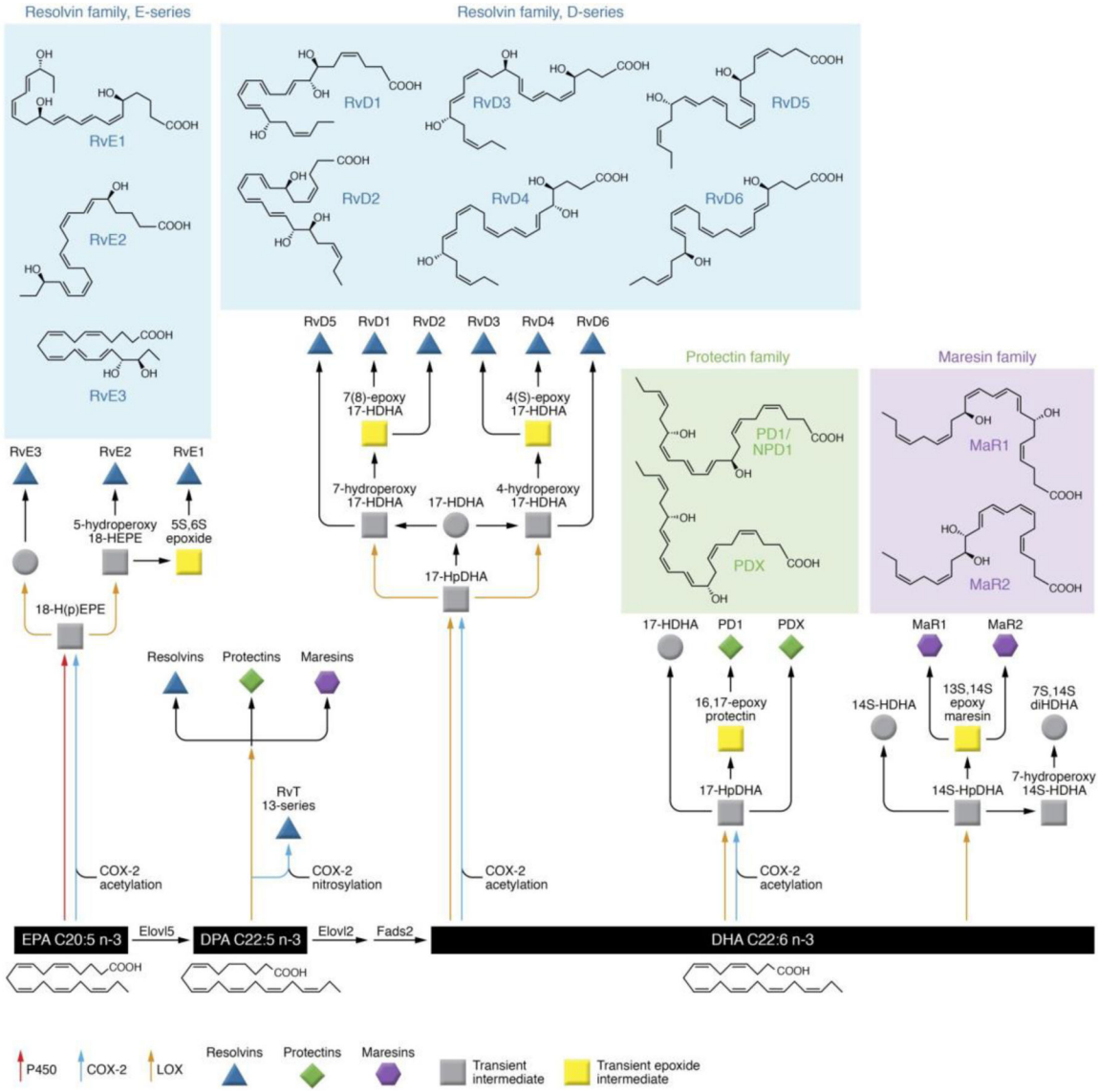

Figure 2. Lipid mediators derived from PUFAs.

Omega-3 fatty acid-derived pro-resolving lipid mediators are produced from endogenous eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), or docosahexaenoic acid (DHA). A variety of enzymes and intermediates create these specialized pro-resolving mediators in the resolution of inflammation. *Original figure reproduced from* Ref. 80.

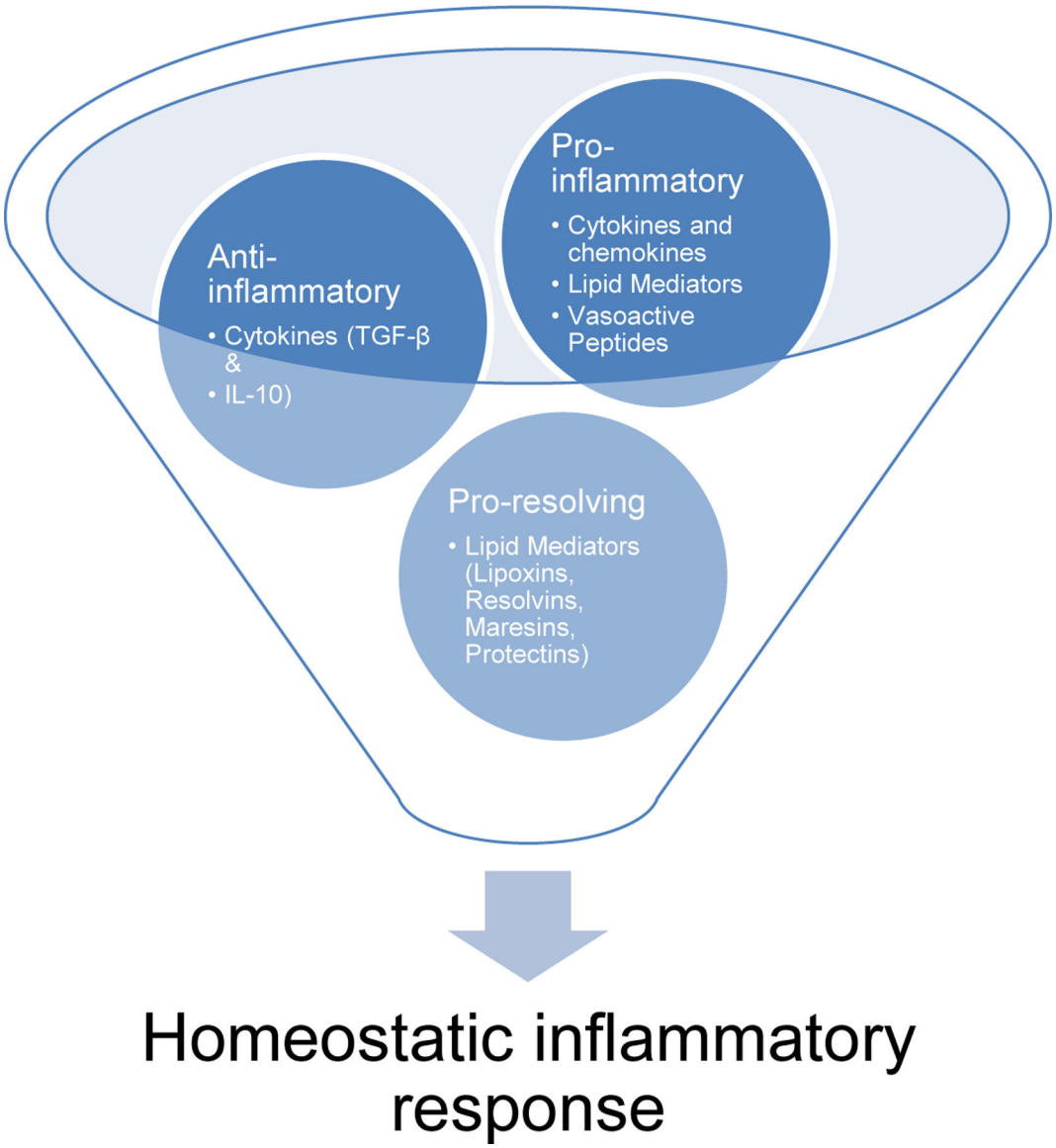

Figure 3. Balanced approach to chronic inflammatory disease treatment, where anti-inflammatory strategies are complemented by endogenous pro-resolving mechanisms.

Chronic rhinosinusitis has been shown to have an increased prevalence in patients with dysfunction of the inflammatory process. To properly resolve this inflammation pro-inflammatory, anti-inflammatory, and pro-resolving processes must be balanced and temporally coordinated to restore a healthy physiological state.

Table 1.

Specialized Pro-Resolving Mediators, their mechanism, and source.

Lipid Mediator	Mechanism of Action	Lipid Source	References
Lipoxin A_4 (LXA_4)	• Increase monocyte infiltration and vascular permeability. • Reduction of neutrophil chemotaxis and clearance via macrophages. • Inhibits the production of reactive oxygen species.	Arachidonic acid (AA)	Shimizu S et al, 2013 [42] Takano T et al, 1998 [43] McMahon B et al, 2001 [44] Levy BD et al, 1993 [45]
Lipoxin B_4 (LXB_4)			
Resolvin D_1 (RvD_1)	• Halts IgE class-switching in plasma cells • Shift macrophages from M1 to M2 phenotype. • Inhibition of NF-kB pathway.	Docosahexaenoic Acid (DHA)	Serhan CN et al, 2012 [47] Krishnamoorthy S et al, 2010 [56]
Resolvin D_2 (RvD_2)	• Shift macrophages from M1 to M2 phenotype		Shan K et al, 2020 [46]
Resolvin E_1 (RvE_1)	• Increases PMN apoptosis • Inhibition of leukotriene activity	Eicosapentaenoic Acid (EPA)	El Kebir D et al, 2012 [49] Yang M et al, 2020 [55]
Resolvin E_2 (RvE_2)	• Activates phagocytosis of PMNs • Enhances production of anti-inflammatory cytokines		Oh SF et al, 2012 [50]
Resolvin E_3 (RvE_3)	• Reduces PMN activity		Isobe Y et al, 2012 [51]
Maresin (MaR1)	• Shift macrophages from M1 to M2 phenotype • Promote tissue regeneration	Docosahexaenoic Acid (DHA)	Serhan CN et al, 2012 [47]
Protectin (PD1)	• Neuroprotective • Reduced NF-kB activity • Enhance phagocytosis • Reduce leukocyte migration		Vidar Hansen T et al, 2022 [48]

Table 2.

Preclinical and Clinical Studies

Trial	Authors	Mediator(s)/enzymes studied	Summary
Preclinical studies			
Lipid mediator class switching during acute inflammation	Levy BD et al. [57]	Lipoxin A_4 (LXA_4)	LXA_4 was shown to be expressed with increased leukotriene levels. This study also showed that LXA_4 reduced PMN migration.
SPMs inhibit human B-cell IgE production	Kim N et al. [58]	Resolvin D_1 (RvD_1)	RvD_1 decreased B-cell differentiation into IgE-producing plasma cells.
Toll-like receptor 7 and production of SPMs	Koltsida O et al. [59]	Resolvin D_1 (RvD_1) & Protectin D_1 (PD_1)	Toll-like receptor 7 can induce PD_1 and RvD_1 synthesis.
Clinical Studies			
Prostaglandin, leukotriene, and lipoxin balance in chronic rhinosinusitis	Pérez-Novo CA et al [28]	15-Lipooxygenase (15-LOX) activity	15-LOX activity was increased in CRS patient. Activity was higher in patients with CRSwNP compared to CRSsNP.
ALOX15 variant and protection against nasal polyps and CRS	Kristjansson RP et al. [60]	ALOX15 gene	Missense mutations in the ALOX15 gene results in lower prevalences of CRS and nasal polyposis.
Genomics of asthma, allergy, and CRS	Laulajainen-Hongisto A et al. [61]	Genome-wide association study	Study showed that there are many mutations associated with risk of CRS.
Altered tissue specialized pro-resolving mediators in chronic rhinosinusitis.	Vickery et al. [7]	LXA_4, LOX, cyclooxygenase (COX)	This study shows significant dysregulations is LOX & COX enzyme families in CRS. It also shows that dysbiosis in the microbiota was associated with dysregulation of LOX metabolites.
Dysregulated metabolism of polyunsaturated fatty acids in eosinophilic allergic diseases	Miyata et al. [65]	Lipoxin A_4 (LXA_4)	LXA_4 levels were decreased in patients with eosinophilic disease.
15-epi-Lipoxin A4, Resolvin D2, and Resolvin D3 Induce NF-kappaB Regulators	Sham HP et al. [68]	Lipoxin A_4 (LXA_4), Resolvin D_2, Resolvin D_3	LXA_4, RvD_2, and RvD_3 were all shown to reduce NF-kB activity.
Resolvin D1 (RvD1) and maresin 1 (Mar1) contribute to human macrophage control	Ruiz A et al. [69]	Resolvin D_1 & Maresin D_1	RvD_1 and Mar_1 were both shown to transition M1 macrophages to their M2 phenotype.
Dietary Fatty Acid Modification for the Treatment of AERD	Schneider TR et al. [71]	EPA & DHA metabolites.	Oral supplementation of omega-3 fatty acids were shown to increase plasma levels of EPA and DHA metabolites as well as increase quality of life scores in CRS patients.
Role of Omega-3 Polyunsaturated Fatty Acids in Treatment of Nasal Polyposis	Attia et al. [72]	Omega-3 fatty acid supplemenetation.	Supplementation of omega-3 fatty acids significantly increased the time for nasal polyp recurrence compared to control.