Role of Lipoxins, Resolvins and Protectins in Mediating Inflammation — Review

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ABSTRACT

This paper reviews the effects of Lipoxins, Resolvins and Protectins on inflammation and why they are promising candidates for resolution of inflammatory process in periodontal disease and application of their role in novel therapies like host modulation in periodontal disease.

Keywords: Arachidonic acid; Eicosapentaenoic acid [EPA]; Docosahexanoic acid [DHA]; Prostaglandins; Apoptosis.

Introduction

Inflammation is an essential biological process for maintenance of tissue homeostasis and recovery from injury or foreign pathogens. Prolonged inflammation, however, can be destructive and maladaptive, leading to disease progression and tissue destruction.1-3 Resolution of inflammation has been well appreciated to be one of the four major outcomes for acute inflammation, along with progression to chronic inflammation, abscess development or scar formation.2,4,5 It was traditionally believed that resolution of inflammation was a passive process, driven primarily by the declining levels of pro-inflammatory mediators over time and down regulating the acute inflammatory response.2,4 The resolution of acute inflammation is complex process which involves several distinct cellular mechanisms. Cell clearance is critical to resolution and is driven both by apoptosis of leukocytes5-7 and recruitment of monocytes that participate in the phagocytosis of apoptotic cells and microbes.6,26 As cell numbers decline, levels of pro-inflammatory cytokines decrease and eicosanoid class switching changes from generating pro-inflammatory lipid mediators (e.g. leukotrienes [LTs] and prostaglandins [PGs]) to anti-inflammatory mediators (e.g., lipoxins [Lxs], resolvins [Rvs] and protectins [Pds]).1-5 This paper review the effects of Lipoxins, Resolvins and Protectins on inflammation and why they are promising candidates for resolution of inflammatory process in periodontal disease and application of their role in novel therapies like host modulation in periodontal disease.

Lipid mediators are important messengers in many physiological processes. The pro-inflammatory effect of many prostaglandins, derived from the essential arachidonic acid during inflammation, is well established. However, there are also anti-inflammatory lipid mediators like Lipoxins, Resolvins and Protectins derived from essential omega-6 and omega-3 polyunsaturated fatty acids (n-3 and n-6 PUFA), which have been shown to control and resolve inflammation in a variety of experimental models of inflammatory disorders and conditions like periodontal disease. Recent research implicates n-6 PUFA–derived Lipoxins and n-3 PUFA–derived lipid mediators such as Resolvins and Protectins were shown to resolve inflammation in experimental models.

Lipoxins: Lipoxins are a series of short lived anti-inflammatory mediators, which are endogenously bioactive eicosanoids, derived from arachidonic acid.8,9 Lipoxins were first described by Serhan, Hamberg and Sammuelson10 as lipoxin A4 [LXA4] and lipoxin B4 [LXB4]. Lipoxins are synthesized by cell-cell interaction and the sequential transformation of PUFA by different lipoxigenases. Cyclooxygenase-2 has an important role in lipoxin formation.11 Acetylation of COX-2 by acetylsalicylic acid modifies the enzyme as lipoxigenase, forming the lipoxin precursor 15- hydroxyeicosatetraenoic acid [15-HETE] from arachidonic acid. From this precursor, leukocyte 5-LO synthesizes 15-epilipoxin A4 or 15-epilipoxin B4, the so called aspirin triggered lipoxins [ATLs] which possess more potent anti-inflammatory effects than LXA4.8

Resolvins: Resolvins are novel oxygenated products generated from omega–3 fatty acid precursors ie, eicosapentaenoic acid [EPA] and docosahexanoic acid [DHA] in the presence of aspirin.12 Resolvins derived from EPA are RvE1 and RvE2, where as Resolvins derived from DHA are RvD1-RvD6.13 These molecules display potent anti-inflammatory and immune regulatory properties.2,5 Resolvin E1 (RvE1) and Resolvin E2 (RvE2), two major products in the family of EPA-derived resolvins from human endothelial cells and PMNs,2,5,14 RvE1 is spontaneously produced in healthy subjects and levels are increased in individuals taking aspirin /or EPA.15 RvE2 is a second member of the EPA-derived family of E-series and shares homology to RvE1.2,16 RvE2 is synthesized by human PMNs in greater amounts and possess equal amount of anti-inflammatory action when compared with RvE1. RvE1 in low doses requires RvE2 as an additive for resolution of inflammation.16,17 Docosahexanoic acid [DHA] derivatives RvD1-RvD6 also possess function of proresolution of inflammation similar to RvE1 and RvE2.17

Protectins (PD1): Docosahexanoic acid [DHA] also serves as a precursor for the biosynthesis of additional bioactive counter-regulatory lipid mediators called neuroprotectin or protectin or resolvin PD1.2,18 PD1 is synthesized by human peripheral blood mononuclear cells and in Th2 CD4+ cells in a LOX-dependent manner. The aspirin-triggered RvD1 (AT-RvD1) and RvD2 are derived from DHA, initiated by 15-LOX or aspirin-acetylated COX-2, respectively. In the absence of aspirin, endogenous DHA substrate is enzymatically converted into 17S alcohol containing series of Rvs (RvD1-RvD4).2,19

Biological activity: Lipoxins (Lipoxin A4 and 15-epi-LXA4) interact with highly specific and distinct G protein-coupled membrane receptors on polymorphonuclear leukocytes to inhibit PMN-mediated increased vascular permeability, chemotaxis, adhesion and migration through the endothelium.20
The LXs also stimulate apoptosis of PMNs and phagocytosis by monocyte-derived macrophages. Aspirin promotes this process and increases the rate of return of the tissue to normal state. The pro-resolving activity of aspirin is exerted not only through the induced synthesis of the lipoxins, but also via the induced synthesis of an additional class of anti-inflammatory lipid mediators known as the resolvins (Rvs) and the protectins (PD1) activation.

**EPA-derived E-series Resolvins:** RvE1 decreases PMN tissue accumulation by blocking human PMN transendothelial migration, inhibition of PMN superoxide anion generation in response to TNFa or the bacterial peptide N-formyl-methionyl-leucylphenylalanine, stimulation of macrophage phagocytosis of apoptotic PMNs, inhibition of dendritic cell migration and cytokine release and upregulation of CCR5 expression on leukocytes. Resolvin E1 (RvE1) decreases the expression of proinflammatory genes such as interleukin-12 (IL-12), tumor necrosis factor alpha, and inducible NO synthetase. Recent studies have revealed that RvE1 is a potent modulator of proinflammatory leukocyte expression molecules, such as L-selectin, and selectively disrupts thromboxane-mediated platelet aggregation. LXA4 and RvE1 regulate physiological inflammation that is beneficial to the host, such as, in wound healing. The RvE1-specific G-protein-coupled receptor was found to be expressed in dendritic cells found to be responsible for the suppression of IL-12 secretion. Pre-treatment with RvE1, in murine model conferred, significant protection from inflammation-induced bone loss in periodontitis. RvE2 has similar functions like RvE1, it stops zymosan-induced PMN infiltration and displays potent anti-inflammatory properties.

**DPA-derived D-series Resolvins:** RvD1 is equipotent to AT-RvD1, limiting PMN infiltration in a dose-dependent fashion. RvD1 is also more resistant to metabolic inactivation than LXA4 which is converted to 17-oxo-RvD1, which is biologically inactive.

**Protectins:** An additional anti-inflammatory lipid derived from DHA is protectin D1 (PD1/NPD1). Aspirin can also trigger the synthesis of an epimeric protectin D1 compound. The (neo) protectins similar to resolvins has anti-inflammatory effects and protects epithelial cells from apoptosis induced by oxidative stress. Protectin D1 inhibit T cell and PMN migration, promote T cell apoptosis, decrease TNF-α and INF-γ secretion.

**Conclusion**

Periodontitis is a chronic inflammatory disease involving large number of molecules, that are produced by the host and microorganisms. These molecules are either proinflammatory or anti-inflammatory in their function. Lipoxins, Resolvins and Protectins possess anti-inflammatory actions, such as inhibition of superoxide anion generation, endothelial transmigration, apoptosis of PMNs and macrophage induced phagocytosis. Host modulation therapy offers the potential for down regulating destructive aspects and upregulating protective aspects of the host response to reduce the periodontal disease progression. Augmenting naturally occurring omega-3 fatty acids in the production of Resolvins and Protectins in the host is to limit inflammation and promote wound healing and regeneration. Development of aspirin triggered production of lipoxins, Resolvins and Protectins in resolution of inflammation will be a possible method in preventing periodontal disease progression and a definitive mode in the application of host modulation therapy.

**Authors Affiliations**


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