



## Role of Resolvins in Periodontal Inflammation-A Review

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### ABSTRACT

*The discovery of resolvins has been a major breakthrough for understanding the processes involved in resolution of inflammation. Resolvins belong to a family of novel lipid mediators that possess dual anti-inflammatory and pro-resolution actions. When inflammation is initiated, goal of host response is to quickly return to homeostasis through rapid elimination of invading leucocytes. Resolution of inflammation is an active process. Cells and events are stimulated to respond, which is quite different from blocking pro-inflammatory pathways. Periodontitis is a chronic multifactorial disease. Various aspects of innate and acquired immunity play role in the pathogenesis of periodontitis. When an inflammatory event is initiated by bacteria, viruses or injury, the goal of the host response is to quickly return to homeostasis through rapid elimination of invading leukocytes. This review summarizes known signaling pathways utilized by resolvins to regulate inflammatory responses associated with the oral cavity.*

**Keywords:** inflammation, resolvins, periodontitis

### INTRODUCTION

Inflammation is an essential biological process for maintenance of homeostasis and recovery from tissue injury or foreign pathogens. Prolonged inflammation, however, can be destructive and maladaptive, leading to disease and tissue destruction.<sup>1</sup> Despite many recent advances in the

treatment of inflammatory disorders, mechanisms for the resolution of inflammation are still poorly understood and provide many new potential therapeutic targets in addressing diseases associated with unresolved inflammation (Gilroy *et al.*, 2004; Serhan *et al.*, 2008).<sup>2,3</sup> Resolution 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. 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 'fizzling out' of the acute inflammatory response. The discovery of resolvins has been a major breakthrough for understanding the processes involved in resolution of inflammation. Resolvins belong to a family of novel lipid mediators that possess dual anti-inflammatory and pro-resolution actions. Specifically, they protect healthy tissue during immune-inflammatory responses to infection or injury, thereby aiding inflammation resolution and promoting tissue healing.<sup>1</sup>

### RESOLUTION AND REPAIR

'Pro-resolving' mediators are readily generated in host tissues. These factors limit leukocyte channelization directly into the inflamed site, reverse the cardinal signs of inflammation such as vasodilation and vascular permeability, and coordinate the clearance of exhausted leukocytes, exudates, and fibrin; eventually leading to the restoration of function. All of these inflammation-resolving processes limit and prevent tissue injury and further progression of acute inflammation into chronic inflammation.

If there is a failure of the host in its ability to eliminate the injury in acute phase, inflammation proceeds to a chronic phase and results in varying degrees of tissue injury. When tissue injury is mild

and confined, necrotic cells will be replaced by new cells via regeneration. If tissue damage is extensive, the process of healing is repair (scarring). When repair takes place, fibrin is not cleared rapidly and efficiently and granulation tissue is formed from surrounding tissue compartments. Later phases of repair involve fibroblast mediated collagen deposition, disappearance of vascular tissues and replacement of these areas by avascular and fibrotic scar tissue.<sup>4</sup>

Thus, in the context of resolution of inflammation, 'acute resolution' leads to regeneration, whereas 'chronic resolution' results in repair. These terms are applicable to periodontal tissue healing. In periodontal disease pathogenesis, similar to other forms of host-mediated tissue injury, such as rheumatoid arthritis and asthma, chronic resolution also leads to ongoing tissue damage through continuous and recurring episodes of acute inflammation. Therefore, the initiation and resolution of inflammation are two parallel phases in chronic inflammation and such pathologies should be defined as 'continuous' inflammatory diseases rather than independent stages.

Until recently it was thought that resolution of inflammation is due to gradual decrease in molecules such as prostaglandins, leukotrienes and interleukins. Now it is clear that resolution of inflammation is affected by a new class of lipid molecules that emerge in late inflammation and are known as lipoxins and resolvins.<sup>5,6</sup> These molecules bind to distinct receptors on the cells which alter the function of the cell leading to resolution and healing. Due to the presence of these lipid

molecules in resolution phase it is clear that the resolution is an active process rather than passive as it was earlier thought. The term resolvins (resolution phase interaction products) was first introduced to emphasize that these are endogenous products possessing anti inflammatory properties.

### ROLE OF ASPIRIN IN RESOLUTION

Aspirin (ASA) is unique among current therapies because it acetylates cyclooxygenase (COX)-2 enabling the biosynthesis of resolvins-containing precursors of endogenous antiinflammatory mediators. Human COX-2 converts docosahexanoic acid (DHA) to 13-hydroxy-DHA (HDHA) that switches with ASA to 17RHDHA which is also proved to be a major route in hypoxic endothelial cells. Human neutrophils transform COX-2-ASA-derived 17R-hydroxy-DHA into two sets of novel di and tri hydroxy products; one initiates via oxygenation at carbon 7 and the other at carbon 4. These compounds inhibit microglial cell cytokine expression and in vivo dermal inflammation and peritonitis at nanogram (ng) doses, reducing 40-80% leukocytic exudates. These results indicate that exudate, vascular, leukocyte and neural cells treated with aspirin convert DHA to novel 17R-hydroxy series of docosanoids that are potent regulators of resolution. These biosynthetic pathways of proresolution lipid mediators utilize omega-3 DHA and eicosapentanoic acid (EPA) during multicellular events in resolution to produce a family of protective compounds, i.e., resolvins and protectins, that enhance proresolution status.<sup>4</sup>

### RESOLVINS AND PERIODONTITIS

Periodontitis is a chronic inflammatory disease caused by the release of immune mediators, resulting in destruction of the alveolar bone and periodontal connective tissue. The process of bone resorption is a result of proteolysis and acid production mediated by osteoclasts. Additionally, in this process, there is a massive expression of vacuolar-type H<sup>+</sup>-ATPase that enables bone degradation. The mechanism by which bone resorption is regulated involves different factors, including PGE<sub>2</sub>, which activates osteoclasts while influencing their number and function. In contrast, RvE1 was found to inhibit osteoclast growth and bone resorption by interfering with its differentiation.

A previous study indicated that topical application of RvE1 to rabbit periodontal tissue conferred dramatic protection against tissue and bone loss associated with periodontitis. In that study, it was also demonstrated that PMNs from localized aggressive periodontitis were refractory to resolving molecules of the lipoxin series. However, PMNs responded to RvE1, which stopped superoxide anion generation by binding at a site that is functionally distinct from the aspirin-triggered lipoxin receptor. These studies revealed the potential of using resolvins for prevention and treatment of periodontal disease. Furthermore, they provide a new role for resolvins in the pathogenesis of periodontal disease.<sup>7</sup>

## CONCLUSION

A large body of recent work suggests that the resolvins, associated with inflammation, are the molecules responsible for the resolution of inflammation. These molecules have been demonstrated to be important in a variety of disease processes, and their therapeutic potential has been identified in a variety of model systems. It has been demonstrated that resolution of inflammation in periodontitis through resolvin mediated pathways offers potential for the prevention and perhaps treatment of periodontal lesions. Future studies need to focus on the applicability of resolvin therapies in humans for the prevention and treatment of the periodontal diseases.<sup>4</sup>

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