Resolution – A Natural Way to Control Inflammation in Periodontal Disease

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ABSTRACT

The periodontal diseases are usually caused by gram-negative bacteria. The neutrophils play an important role in the destruction of host tissues in periodontal disease. Pro-inflammatory mediators such as prostaglandins and leukotrienes are balanced by counter-regulatory signals provided by pro-resolving lipid mediators. This short review discusses the role of these mediators and the possibility of development of new therapeutic strategies for the control of neutrophil mediated tissue injury in periodontal disease.

Key words: Resolution; Resolvins; Lipoxins; Periodontitis

Inflammation is an important defense mechanism to combat the threat of bacterial infection. Inflammatory mechanisms are responsible for the development and progression of most chronic diseases associated with aging and periodontal disease. Although immune-inflammatory responses to infection and injury are necessary for survival of the host, inflammatory processes can also lead to tissue damage and chronic disease. This short review discusses the role of these mediators and the possibility of development of new therapeutic strategies for the control of neutrophil mediated tissue injury in periodontal disease.

There is distinction between anti-inflammation and resolution; anti-inflammation is pharmacologic intervention in inflammatory pathways, whereas resolution is biologic pathways restoring homeostasis. Evidence suggests that chronic inflammatory periodontal disease involves a failure of resolution pathways to restore homeostasis. Proof-of-concept studies in the 1980s demonstrated that pharmacologic anti-inflammation prevented and slowed the progression of periodontal diseases in animals and man. However, the side-effect profile of such therapies precluded the use of non-steroidal anti-inflammatory drugs or other enzyme inhibitors or receptor antagonists in periodontal therapy. The isolation and characterization of resolving agonist molecules has opened a new area of research using endogenous lipid mediators of resolution as potential therapeutic agents for the management of inflammatory periodontitis. Controlling or augmenting these mechanisms may lead to the development of novel treatment strategies for managing chronic diseases like periodontitis.

Pro-resolving Lipid Mediators: Resolution of inflammation is an active process, rather than a passive decay of proinflammatory signals, requiring the activation of specific mechanism that restore homeostasis. Resolution pathways are initiated following an acute inflammatory response. Resolving lipid mediators include lipoxins (LX) that are produced from the metabolism of endogenous arachidonic acid (AA) and resolvins that are derived from dietary omega-3 polyunsaturated fatty acids (omega-3 PUFA). Lipoxins and maresins are the currently discovered pro-resolving molecules derived from omega-3 PUFA.

Lipoxins: Release of arachidonic acid (AA) from cell membrane generates lipid mediators of inflammation like eicosanoids, prostanoids, prostacyclins and leukotrienes. On stimulation of G-protein receptors in the cell membrane triggers the release of AA from phosphatidylycholine by the enzyme phospholipase A2. The free AA is metabolized by cyclooxygenase-1 (COX-1) and (COX-2) dependent pathways that result in the generation of prostanoids, or a lipoxigenase (LO) dependent pathway. The three LOs are cell specific; SLO expressed by myeloid cells, 12-LO is expressed by platelets, and 15-LO is expressed by endothelium and epithelium. The end products of the LOs are 5, 12 or 15 hydroxyeicosatetraenoic acid (HETE), the 5-HETE is further metabolized to leukotrienes (LT). Prostanoids and leukotrienes produce pathophysiologic response associated with periodontal disease.

In the normal resolution program, a “classic switch” occurs within neutrophils giving rise to the synthesis of proresolving molecules. Proresolving lipid mediators are produced from AA through mucosal and vascular cell-cell interactions where 15-S-H(p)ETE is produced by oxidation of AA by 15-LO followed by 5-LO oxidation of the same molecule. The products of lipoxins (LX) are lipoxin A4 (LXA4) and lipoxin B4 (LXB4). The lipoxins produced bind to FPR1 also known as the FMLP receptor, to stimulate the resolution of inflammation. The actions of lipoxin are the limitation of neutrophils migration into sites of inflammation, promotion of neutrophil apoptosis, and activation of monocytes to non-phlogistic phenotype.

Aspirin Triggered Lipoxin (ATL): Aspirin plays an important role in the biology of resolution of inflammation. Aspirin inactivates COX-2 by acetylation of the enzyme creating a new active enzyme. Aspirin modified COX-2 is 15R LO. The product of this aspirin triggered pathway is 15R-H(p)ETE, which is further metabolized by neutrophil 5-LO to yield aspirin triggered lipoxin (ATL) and resolvin compounds that are long lasting and more potent than endogenous resolvins and lipoxins. The inhibition of COX-2 by non steroidal anti-inflammatory drugs (e.g. rofecoxib) may attenuate signs of acute inflammation, and the reduction of PGE, would fail to generate proresolving lipoxin which are needed for restoring homeostasis in tissues.

Resolvins and Protectins: While lipoxins are produced from endogenous omega-6 fatty acid substrate. Another family of proresolution agonists are metabolized by the same LO en-
zyme systems from dietary omega-3 poly unsaturated fatty acids (PUFAs) i.e., the resolvin and protectins. The resolvin and protectins are derived from eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the major omega-3 PUFAs found in fish oil. EPA is the substrate for resolvin of the E series and DHA the resolvins D series as well as protectins or neuro-protectins in neural tissue.4

The term resolvin, resolution phase interaction products, was introduced to signify that the new structures are endogenous, local-acting mediators possessing potent anti-inflammatory and immunoregulatory properties.13,19,20 At the cellular level, these include reducing neutrophil infiltration and regulating the cytokine-chemokine axis and reactive oxygen species, as well as lowering the magnitude of the inflammatory response.21 The protectin family and specifically the term neuro-protectin D1 when generated in the neural tissue were introduced, has very potent anti-inflammatory property and these mediators are considered to play a key role in many inflammatory diseases like Alzheimer’s disease4 and periodontitis. Resolvins are useful in inhibiting and resolving neutrophil infiltration, driving neutrophil apoptosis, and attracting non-phlogistic monocytes. Resolution macrophages exhibit enhanced phagocytosis of apoptotic neutrophils and enhanced clearance of bacteria at mucosal surface promoting wound clearance and return to homeostasis.23

Lipid Mediators Class Switching: Eicosanoid class switching refers to changes in production within the arachidonate derived family, like prostaglandin and leukotriene, to lipoxins.21,24 Late in the inflammatory process when there is a high concentration of cells containing lipoxigenases and corresponding proinflammatory products like PGE2,a classic switch may occur within neutrophils. This classic switch gives rise to the synthesis of proresolving molecules.24 Lipoxins, specifically LX4A4 and LX4B, as well as their aspirin-triggered forms, stop further neutrophil entry into the exudates as well as counter-regulate the main signs of inflammation.21 As new neutrophils parachute into exudates the older and apoptotic neutrophils must be removed from the site in a timely fashion for inflammation to resolve. Once neutrophils enter an exudates, they interact with other cells (such as other leukocytes, platelets, endothelial, mucosal epithelial, fibroblasts) in their immediate vicinity and are able to perform transcellular biosynthesis to produce lipoxins and eventually new mediators. The process of transcellular biosynthesis is defined as the generation of new bioactive compounds that neither cell type can produce on its own.25 It is demonstrated that neutrophils switch their phenotype in that they change the profile of lipid mediators that they produce depending on their local environment.21 During the course of inflammation and complete resolution, mediator switching also occurs between families of lipid mediators, namely from eicosanoids to resolvin of the E and D series as well as protectins.

Potential of lipid molecules as therapy: Lipoxins are rapidly metabolized and unstable making them poor pharmacologic candidates in their native form. The potential of aspirin triggered analogs(ALTα) as pharmacological anti-inflammatory agents was examined in animal models of neutrophil mediated tissue injury.26 On application of ResolvinE1 in rabbit model for treating periodontitis, histologically revealed no inflammatory changes, osteoclast formation or bone loss and temporal shift in the microflora in oral biofilm were also observed.6 None of the resolution agonists has to date, been approved for clinical use, although several are in development. In a pilot trial27 80 subjects with moderate to severe periodontitis were treated with either scaling and root planning followed by a regimen of 900mg of EPA/DHA with 81mg aspirin daily for 6 months, or the same mechanical regimen and placebo tablets. Addition of resolving generating dietary supplement to standard periodontal therapy provided an added benefit reducing probing depth and increasing clinical attachment and providing reduction in inflammatory mediators in saliva.28

Conclusion
In conclusion the primary etiological factor for periodontal disease was bacterial origin. The pathogenesis of periodontal disease includes excessive host inflammatory response and inadequate resolution of the same. The pro-resolving lipid mediators are useful in controlling the inflammation and restoring the tissue to homeostasis.

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References


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