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Commentary

New directions in host modulation for the management of periodontal disease

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Abstract

Background: New strategies for periodontal disease management have been emerging as more is learned about the role of the host response. Our increasing understanding of inflammation and its resolution has opened the door to the study of new periodontal treatment strategies. This commentary examines periodontal disease in light of a new understanding of the role of inflammation in disease expression, thus setting the stage for the development of new prevention and treatment strategies of a widespread disease.

Methods: We examined current publications and focused on articles relating to anti-inflammatory and pro-resolution mechanisms in periodontal disease.

Results: Recent research has examined the inflammatory and resolution cascade in greater detail while looking at endogenous and exogenous mediators that can be utilized to achieve therapeutic end-points. The possible introduction of ''resolution indices'' for drug testing warrants a new look at pharmacologic agents that might have been overlooked for their beneficial effects in periodontal disease treatment.

Conclusion: The emerging awareness of inflammation and its control in periodontal disease management underscores the importance of exploring inflammatory pathways and mediators, thus exploring new ways to control inflammation. This direction of research promises a new era in drug discovery and therapeutics for periodontal disease treatment.

Key words: anti-inflammatory; drug discovery; inflammation; periodontitis; resolution

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Commentary

Over the last 30 years, the understanding of the nature of periodontal disease causation and pathogenesis has changed dramatically. Resolution of acute inflammation, mainly by the exodus of neutrophils from the tissues, has long been thought to be a passive process. Recent research (Schwab et al. 2007, Serhan et al. 2007) has identified distinct biochemical pathways that are actively turned on during inflammation in the resolution phase, and thus points to an ''active'' biochemical resolution. From a histological standpoint, this resolution phase has been aptly defined as the interval from maximum neutrophilic infiltration to the point when they are lost from the tissue (Serhan et al. 2007). Anti-inflammation is therefore not the same as resolution of inflammation. Consequently, our approach has evolved from blocking inflammation to moderating it. The importance of this research direction can be accessed from the recent AAP Boston conference that brought together researchers and clinicians across several disciplines to better understand the role of inflammation and resolution (Kornman & Van Dyke 2008).

Acute inflammation undergoes an active process of resolution that is necessary for tissue protection, and the endogenous molecules, resolvin E1 (RvE1) and protectin D1, play the role of resolution agonists (Schwab et al. 2007). This stage for resolution is set early in the activation phase of the inflammatory response (Winsauer & de Martin 2007). Similar pro-resolution properties have been found for retinoid X-receptors in human epidermal cells (Kalsotra et al. 2007), activated macrophages (Martinez et al. 2008), and lipoxins (Romano 2006). Therapeutic manipulation of fibroblasts (Flavell et al. 2008) and their biologically

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active products is an emerging concept in treating cancer and is likely to provide a novel method to achieve improved control of chronic inflammatory disease, with possible applications in the field of periodontitis.

When we conducted an online PubMed search using the search words ''Periodontitis, Anti-Inflammatory'', one meta-analysis assessing efficacy of anti-inflammatory drugs in the treatment of periodontitis was found (Reddy et al. 2003). When a PubMed search similar to the first one was conducted using the search words ''Resolution of inflammation, periodontitis'', no meta-analysis reports were found, but we did find several in vitro studies and review articles (Kantarci et al. 2006, Nassar et al. 2007, Serhan et al. 2007, Van Dyke 2007) examining the concept of resolution of inflammation in periodontitis. The lack of a meta-analysis is not surprising, given that this is a newly emerging topic of research interest. However, a comparison between these search results might suggest that several previous studies on inflammation failed to delineate and attribute the clinical effects of treatment independently to inflammation or resolution. For instance, some drugs like aspirin that have been widely used for their perceived reduction in or blocking of inflammation might in fact be working because of their combined anti-inflammatory and pro-resolution effects (Serhan et al. 2007).

Current understanding of periodontal disease initiation states that the presence of pathogens in the periodontal pocket leads to pocket formation with further tissue destruction. Van Dyke (2007) propose that by introducing ''resolving agents'', perhaps the resolution of inflammation leads to disappearance of the pathogenic bacteria by removal of their food source. If this hypothesis is proven correct by further research, it would indeed lead us to rethink our clinical treatment strategies. By moving towards drugs that promote resolution, rather than just anti-inflammation, we may be able to harness the advantages in the inflammatory cascade, while leading to a speedy return to homeostasis, and health. The use of some of these pro-resolution agents has already been tested in animal models (Hasturk et al. 2007), where the use of RvE1 has been shown to markedly reduce periodontal inflammation, with regeneration of bone to pre-ligature height, and regeneration of cementum and an organized periodontal ligament.

Bannenberg et al. (2005) have proposed a set of resolution indices in an attempt to set benchmarks to assess the impact of pro-resolving agents. It is possible that these indices might introduce new perspectives to the field of drug research. Needless to say, the optimum drug regimen would have to be developed after delineating the exact mechanisms between acute and chronic inflammatory processes. This, in turn, might potentially translate into arresting periodontal disease before it becomes a chronic process.

If pro-resolving agents continue to be developed, then a significant clinical implication would be a change in how we differentiate between the clinical signs of inflammation or resolution, and use this information in subsequent therapy. We are traditionally attuned to identifying inflammation solely by its presence or absence, using bleeding on probing as a clinical parameter. The introduction of a new ''resolution'' parameter that does not solely depend on the absence of inflammation might add an interesting concept to periodontal disease diagnosis and treatment. Development of drugs based on endogenous mediators inherent to resolution (Gilroy et al. 2004) may represent a new strategy in anti-inflammatory treatment in general and periodontal therapy in particular. However, with the exception of some drugs that target apoptosis (Murphy et al. 2003), and drugs like methotraxate, sulphasalazine, and FK506 (Hasko & Cronstein 2004) that target adenosine, we are not aware of many commercially available drugs that utilize the resolution pathway. As more randomized clinical trials examining resolving agents become available, we will continue to move towards a commercially available ''pro-resolution'' drug for periodontal disease.

In conclusion, the emerging awareness of the control of inflammation in periodontal disease management underscores the importance of exploring inflammatory pathways and mediators and thus better understanding possible new interventions. If the control of inflammation can be clinically effective, it might question the temporal relation of increase in microbial numbers and deepening of a periodontal pocket, and merit further analysis of microbial pathogenesis. Lastly, the possible introduction of ''resolution indices'' for drug testing might warrant a second look at some drugs that might have been overlooked for their beneficial effects in the treatment of periodontal disease. Well-designed studies are needed to clarify and understand this fascinating research direction in periodontal medicine.

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Clinical Relevance

Scientific rationale for the study: This commentary examines periodontal disease in the light of the new understanding of the role of inflammation and resolution of inflammation in disease expression.

Principal findings: Anti-inflammation is not the same as resolution of inflammation. There appears to be clear evidence for ''active'' biochemical resolution, and suggests a new frontier in drug discovery and therapeutics for periodontal disease treatment.

Practical implications: This article highlights a new era in the development of new prevention and treatment strategies for the clinician for the management of periodontal disease.