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RESOLUTION OF INFLAMMATION- UNRAVELING MECHANISTIC LINKS BETWEEN PERIODONTITIS AND CARDIOVASCULAR DISEASE

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Periodontitis is considered a gram negative infection. Extensive data accumulated in recent years point to the fact that the tissue destruction that characterizes periodontitis is mediated by the host response; it is not due to direct actions of bacterial virulence factors. Hence, periodontitis is now being characterized as an inflammatory disease induced by microorganisms.

Interestingly, many other common diseases of man are now being considered inflammatory in nature. In particular, cardiovascular disease, long characterized as a lipid disease because of the end stage pathology, is now known to have a large inflammatory component. In recent years, epidemiologic studies have ascertained an association between cardiovascular disease and other inflammatory diseases, in particular periodontal diseases. Given the prolonged nature of the pathogenesis of CVD, it has been difficult to demonstrate cause and effect in this association. To that end, we sought to investigate the relationship between CVD and periodontitis longitudinally in an animal model. New Zealand White Rabbits were fed a 0.5% fat diet for 13 weeks. This is known to cause atheromatous changes in the large arteries of the animals. In the experiment, periodontitis was induced with a ligature and *P. gingivalis*, while the other half maintained a normal periodontium. Using the size (area) of the atheromatous lesion as the primary outcome, the animals that had periodontitis exhibited double the atheroma formation of the controls. These data provide direct longitudinal evidence that suggests that periodontal inflammation can impact upon the progression of CVD. Further investigation was unable to isolate bacteria from the arterial lesions; however, it was demonstrated that isolated inflammation was able to induce upregulation of the inflammatory response. These data suggest that the impact of infection is not at the level of bacteremia and direct stimulation of arterial endothelium, but rather local inflammation inducing a systemic elevation of inflammation.

It has become clear in recent years that periodontitis is an inflammatory disease that is initiated by the oral microbial biofilm. This distinction implies that it is the host response to the biofilm that destroys the periodontium in the pathogenesis of the disease. As the understanding of pathways of inflammation has matured, a better understanding of the molecular basis of resolution of inflammation has emerged. Resolution of inflammation involves an active;

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agonist mediated well-orchestrated return of tissue homeostasis. There is an important distinction between anti-inflammation and resolution; anti-inflammation involving pharmacologic intervention in inflammatory pathways, resolution is physiologic pathways restoring homeostasis. A growing body of research suggests that chronic inflammatory periodontal disease involves a failure of resolution pathways to restore homeostasis. Proof of concept studies in the 1980's 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 use of NSAIDS or other enzyme inhibitors or receptor antagonists in periodontal therapy. The isolation and characterization of resolving agonist molecules, such as lipoxins, resolvins and protectins, has opened a new area of research using endogenous lipid mediators of resolution as potential therapeutic agents for the management of inflammatory periodontitis. Work in animal models of periodontitis has revealed the potential of this therapeutic approach for prevention and treatment and forced reconsideration of our understanding of the pathogenesis of human periodontal diseases.

In the same rabbit model of periodontitis, it was demonstrated that topical application of RvE1, an eicosapentaenoic acid (EPA) ω -3 fatty acid derivative, prevented the onset of *P. gingivalis* induced periodontitis. Further experiments demonstrated that RvE1 treatment of established disease reversed the inflammation and regeneration of lost tissues was documented. These data suggest that control of inflammation with receptor agonists that drive a return to tissue homeostasis may provide a rational treatment strategy for periodontitis that enables the host to reverse disease and regenerate lost tissues.

The next relevant question is whether the relationship can be experimentally documented. In order to determine the relationship between the innate inflammatory response and susceptibility to CVD and periodontitis, a 15-lipoxygenase (15-LO) transgenic rabbit was engineered. The overexpression of 15-LO leads to a rise in the product 15-HETE, which is rapidly metabolized by myeloid 5-LO into lipoxin A₄. The resulting phenotype is a rabbit with increased circulating LXA₄ that exhibits a lower innate inflammatory response. Interestingly, the lower response is not characterized by impaired innate immunity, but rather by reduced tissue damage. In other words, the response is not excessive. Repeating the CVD induction with high fat diet and periodontitis induction experiments in the transgenic animals revealed an interesting phenotype. The transgenic animals were resistant to induction of CVD and protected against development of periodontitis. From these data we were able to conclude that inflammation plays an important role in the pathogenesis of both periodontitis and cardiovascular disease; control of the inflammatory response prevents both periodontitis and early vascular changes in the rabbit model, and control of the inflammatory response (or lack of it) may be the link between the pathogenesis of periodontitis and cardiovascular disease.