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Review Article

Model of Periodontal Pathogenesis: A Comprehensive Review

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ABSTRACT
Periodontal disease (PD) is one of the most common chronic inflammatory diseases affecting humans. It is of multi-factorial origin where host, environment and bacterial factors interplay to initiate immune- inflammatory response that causes most of the soft and hard tissue destruction. Our knowledge regarding the pathogenesis of periodontal disease still remains unclear. The advanced models of pathogenesis will aid in further research and may help in the extrapolation of this data to clinical scenarios. Hence; we aim to summarize some of the important aspects of periodontal pathogenesis models.
Key Words: Periodontal diseases, Model, Periodontal pathogenesis.

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INTRODUCTION

Research into the pathogenesis of disease has traditionally involved a reductionist approach in which discrete inflammatory pathways and processes are investigated to elucidate underlyingmechanisms.With advances in genomic, epigenetic, proteomic, and metabolomic capabilities, an increased interest has emerged in a biologic systems approach to define the complex regulatory networks that result in health or disease.[1] The biologic networks may be implemented in executable models that respond to perturbations in the system, or they may be captured as conceptual models to provide a structural framework for better communications of relationships among data as they relate to pathogenesis.

Periodontitis is a complex disease in which disease expression involves intricate interactions of the biofilm with the host immune-inflammatory response and subsequent alterations in bone and connective tissue homeostasis.[2-4] As such, conceptual models of the pathogenesis of periodontitis may benefit from a systems approach, in which biologic-mechanisms are studied and interpreted in a hierarchical set of functional modules, such as the microbial ecosystem or the immune-inflammatory response, which may be modified by factors (e.g., smoking) that operate at the patient level. A model of the pathogenesis of periodontitis based on systems biology approaches should allow investigators to better communicate the interrelatedness of variousbiologic components involved in the initiation and resolution of disease. This article attempts to highlight selected key steps in the evolution of our concepts of periodontal pathogenesis and to define how future models are likely to evolve based on the new technologies.[5]

ANIMAL MODELS

Experimental studies conducted in monkeys are highly relevant for human clinical practice as they present comparable anatomy and develop similar periodontal diseases with similar clinical symptoms. However, experimental research in monkeys requires a strong ethical justification of their care and use and should take into account the purchasing, transportation and housing expenses of these animals over long periods. The selection of these animals was based on similar pathologies and the ease of surgically created clinically relevant defects. Experimental periodontal defects may be obtained in three different ways:

(i) The acute defect model
(ii) The chronic defect model
(iii) The acute/chronic defect model.

In the acute model, all defects are surgically-induced by removing surgically all the periodontal components (bone, cementum and periodontal ligament). Reproducible defects in experimental and control sites are created. In the chronic model, lesions are obtained by placing orthodontic elastics, silk sutures or ligatures around teeth during 12 to 20 weeks, depending on the type of animal studied. These defects are deeper in the interproximal spaces than in the buccal or lingual surfaces. In the combined acute/chronic model, the defects are surgically-created and ligatures are placed to ensure calculus accumulation and to prevent spontaneous regeneration of the defects. Different animal models used in periodontal research based on pathogenesis of periodontal disease are non-human primates, dogs, minipigs, ferrets and hamsters. They all have showed excellent results during experimental studies. These animal models are also used in periodontal research based on periodontal treatment modalities.[6]

MODEL FOR PERIODONTITIS PATHOGENESIS

Meyle J et al presented a contemporary model of periodontitis pathogenesis based upon a circular relationship between the periodontal biofilm and the inflammatory immune response. Implicit in the model is that the transition from health to gingivitis, and ultimately to periodontitis, is associated with evolution of a health-promoting biofilm, to one of incipient dysbiosis and then to one of frank dysbiosis, and at the same time the host's inflammatory response transits from being proportionate and pro-resolving, to proportionate/nonresolving and then to disproportionate/nonresolving. Unlike the classical paradigm of a pathogenic microflora inducing inflammation, we now recognize that inflammation also contributes to the biofilm structure and function and there is a need for metagenomic studies to start defining what functional characteristics of the biofilm render it pathogenic as opposed to health promoting. At the same time, pathogenic roles for viruses are emerging, either as priming agents of host immune cells or as co-infectors alongside bacteria, conspiring together to deregulate host-defence systems. It is also becoming clear that the hosts' periodontal armamentarium against dysbiosis includes diverse cell types, epithelial cells, dendritic cells, natural killer cells, T- and B-lymphocytes and neutrophils, all of which carefully orchestrate an appropriate response to the biofilm and its components. There are likely to be a multitude of pathways to dysregulation of local host immunity within the periodontium that may arise when such a complex series of highly coordinated signalling events is necessary to maintain tissue homeostasis. The key features of immune disruption in periodontitis include excessive inflammation that fails to resolve and becomes chronic and self-destructive in nature, generating an environment that favors pathogenic bacteria.[7]

POLYMICROBIAL SYNERGY AND DYSBIOSIS (PSD) MODEL OF PERIODONTAL DISEASE PATHOGENESIS

A significant body of evidence based on cultural analyses of periodontal lesions combined with in vitro studies of infection along with animal models of disease had implicated the pathogenic triumvirate of P. gingivalis, Tannerella forsythia, and Treponema denticola as the etiological agents of chronic periodontitis. However, more recent molecular microbiome studies show that the periodontal microbiota is more heterogeneous and diverse than previously thought, with a number of newly recognized species showing a good correlation with disease status. Novel disease-associated species include the Gram-positives: Filifactoralocis and Peptostreptococcus stomatis and other species from the genera Prevotella, Megasphaera, Selenomonas, Desulfobulbus, Dialister, and Synergistetes. Moreover, microbiome studies often show that the organisms of the classical triad are not numerically dominant at disease sites. Recognition that P. gingivalis can be a low-abundance member of the disease- associated microbiota.

The synergistic pathogenicity of periodontal organisms in animal models has been recognized for some time and nutrient transfer among P. gingivalis and other species such as T. denticola is well defined. Indeed, co-culture of P. gingivalis with T. denticola induces an alteration in P. gingivalishemin uptake strategies and changes in the abundance of enzymes involved in glutamate and glycine catabolism. P. gingivalis can provide a source of free glycine and isobutyric acid for T. denticola growth, while T. denticola produces succinic acid which enhances growth of P. gingivalis. Polymicrobial synergy extends well beyond cross- feeding, however, and through sophisticated signalling mechanisms microbial communities are tightly integrated and capable of collectively regulating activities including expression of virulence factors such as proteases.

The PSD model is also consistent with a novel approach for the treatment of periodontitis. Specifically, it predicts that the most promising strategies should be those aiming to restore homeostasis rather than to perform "infection control" through antimicrobials. One such option is community manipulation, e.g., to favor the growth of organisms that are antagonistic to P. gingivalis and/or to reduce the levels or activity of its accessory pathogens, such as S. gordonii.

ANIMAL MODELS FOR PORPHYROMONAS GINGIVALIS-MEDIATED PERIODONTAL DISEASE

Porphyromonas gingivalis is one of the principal pathogens in the development of adult periodontitis. Several different animal models have been used to evaluate the complex interactions between P. gingivalis and the host and these have been an important research tool for studying the pathogenesis of P. gingivalis mediated periodontal diseases. Finding an animal model of periodontal disease that reproduces all aspects of

human disease is an impossible goal. However, we can access models to look at very well-defined aspects of periodontal disease, such as etiology, the role of specific virulence factors, mechanisms of colonization, effects of cells and inflammatory mediators on tissue responses, the role of other infections in periodontal disease and the role of risk factors in periodontal disease. Very well-defined questions can be asked of certain models that are well chosen and well controlled (e.g. transgenic mice). For example, the role of the P. gingivalis proteases and the involvement of interleukin 1 (IL-1) and tumor necrosis factor (TNF) in P. gingivalis pathogenesis can be addressed in various animal models. With a complex disease such as periodontal disease, in vitro experiments are very important but must be evaluated in well-controlled in vivo animal experiments. Each of the different models is important for studying specific aspects of disease. Thus, many different models are needed, with each contributing to the understanding of a different aspect of disease and P. gingivalismediated pathogenesis. It is also apparent that additional models are needed to study tissue regeneration, implants and therapeutic modalities.

Wang and Stashenko have used a rat model to identify the mediators that stimulate bone resorption following infection. This model was designed so that active (rapid) and chronic (slow) phases of bone destruction could be distinguished. Pulpal exposure, followed by infection from the oral environment, was used to induce bone resorption. These studies revealed that IL-1a is the primary proinflammatory cytokine involved in periodontal disease pathogenesis.[4]

Recent studies indicate that periodontal disease might confer a risk for pre-term low birth weight. The effects of P. gingivalis on pregnancy have been studied in hamster models. Collins et al. found that LPS from P. gingivalissignificantly reduced the fetal weight, suggesting that maternal exposure to P. gingivalis LPS can have harmful effects on the developing fetus. It has also been shown that fetal growth retardation and embryo lethality are significantly correlated with increases in PGE2 and TNF-a occurring after P. gingivalis challenge. There are recent reports of the association between cardiovascular disease and periodontal disease and it will be critical to develop animals that will enable investigators to determine the pathogenic potential of P. gingivalis in models of cardiovascular disease.[8- 12]

CONCLUSION

Over the past 50 years, a number of conceptual models describing the pathogenesis of periodontal disease have been presented based on existing knowledge at the time. The more recently explored biologic systems approach to modeling holds promise for revolutionizing conceptual models of the past by providing a comprehensive view of the disease process as a complex regulatory network.

Genomic, proteomic, and metabolomic data related to periodontal diseases are being collected. When these data are combined with knowledge of even a limited set of environmental and genetic factors contributing to periodontitis, we should be able to build more robust models of the pathogenesis of periodontal diseases.

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