

Periodontal Vaccines - A Review

Abstract

Periodontal disease, as a polymicrobial disease, is globally endemic as well as being a global epidemic. It is the leading cause for tooth loss in the adult population and has been positively related to life-threatening systemic diseases such as atherosclerosis and diabetes. As a result, it is clear that more sophisticated therapeutic modalities need to be developed, which may include vaccines. Up to now, however, no periodontal vaccine trial has been successful in satisfying all the requirements; to prevent the colonization of a multiple pathogenic biofilm in the subgingival area, to elicit a high level of effect or molecules such as immunoglobulin sufficient to opsonize and phagocytose the invading organisms, to suppress the induced alveolar bone loss, or to stimulate helper T-cell polarization that exerts cytokine functions optimal for protection against bacteria and tissue destruction. This article reviews all the vaccine trials so as to construct a more sophisticated strategy which may be relevant in the future. As an innovative strategy to circumvent these barriers, vaccine trials to stimulate antigen-specific T-cells polarized toward helper T-cells with a regulatory phenotype (Tregs, CD4+, CD25+, FoxP3+) have also been introduced. Targeting not only a single pathogen, but polymicrobial organisms, and targeting not only periodontal disease, but also periodontal disease triggered systemic disease could be a feasible goal.

Key Words

Immunization; periodontitis; vaccines

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INTRODUCTION

Periodontal disease refers to the processes of destruction of the peri-tooth structures that support the teeth. These are composed of the gingiva, the periodontal ligament, the cementum, and the alveolar bone. The chronic destruction of these supporting tissues leads to the eventual loss of teeth and hence partial or full edentulism. Epidemiological studies reveal that more than two-thirds of the world's population suffers from one of the chronic forms of periodontal disease. Recent recognition of the importance of periodontal disease and its impact on the perpetuation and management of systemic diseases calls for a global effort to control periodontal disease.^[1] The current concept of etiopathogenesis of periodontal disease includes a multifactorial model in which the essential components for the disease causation includes host associated factors, genetic predisposition, immune system dysfunction and environmental factors, such as the presence of virulent periodontal pathogens

(bacteria or viruses) in the form of dental biofilm. Hence, any intervention to arrest or prevent the progression of periodontal disease would include combination approaches, including that of host immune modulation and pathogen-specific approaches. Periodontal pathogens associated with periodontitis predominantly are gram-negative, anaerobic bacteria namely *P. gingivalis*, *A. actinomycetemcomitans*, *T. denticola* and *T. forsythus* etc. Thus, various immunization approaches both as active and passive immunization, against periodontal pathogens have been explored either using and the whole organism or specific virulence factors.^[2] Till date, no preventive modality exists for periodontal disease and treatment rendered is palliative. The availability of periodontal vaccine would not only prevent or modulate the course of periodontal diseases, but also enhance the quality of life of people for whom periodontal treatment cannot be obtained easily.^[3] The purpose of this review article is to discuss the

various avenues associated with periodontal vaccine.

PERIODONTITIS AS A POLYMICROBIAL INFECTION

Traditional concepts of the etiology and initiation of periodontal disease stem from the observation that gingival inflammation ensues from the sequential and quantitative microbial load accumulating in the gingival sulcus as an organized biofilm known as bacterial plaque. The current concept emerges from extensive research findings on the polymicrobial nature of the associated biofilm. This has led to the notion that biofilm quality is the critical factor in the pathogenesis of periodontal disease. Indeed it is now thought that periodontal disease is a specifically combined infection of polymicrobial Gram-negative anaerobic bacteria, including *P. gingivalis*, *T. denticola* and *T. forsythia*, and *A. actinomycetemcomitans*, all of which have been proposed as predominant pathogens, exclusively or synergistically with other bacteria, including *P. intermedia*, *Campylobacter (C.) rectus*, *Fusobacterium (F.) nucleatum*, and herpes virus.

Although periodontal diseases are primarily initiated and perpetuated by mixed biofilm (possibly also including viruses), other factors including host-associated factors, genetic predisposition, immune dysfunction, and environmental factors can exacerbate the disease. Thus, a combined strategy, targeting both specific pathogenic species and the host immune response would have to be adopted for the sophisticated management of the compromised subject.^[2,3]

BASICS OF VACCINATION

Vaccination is a process that induces specific immune resistance to a bacterial or viral infection. It is the development of immunity or resistance to infection, after a secondary response (booster) that is adequate to consider the individual immune to a subsequent infection.^[4] The foremost step in vaccine development is identification of an antigenic component from various organisms that can provide immune protection. Antigens of infectious pathogenic bacteria and viruses have been targets for a variety of vaccines against a number of infectious diseases.^[3,4] The vaccination can be of the following types: Active immunization: Here, an individual immune system is stimulated by administering killed or live attenuated products derived from micro-organisms; Passive immunization: Here, the antibodies formed in one individual are transferred to another; and DNA

vaccination: Here, DNA plasmids encoding genes required for antigen production are transferred to an individual. The characteristics of an effective vaccine include: safety, protectivity, the ability to provide sustained protection, the ability to produce neutralizing antibodies, and stimulation of protective t-cells.^[4] In the early twentieth century, three periodontal vaccines were employed which include pure cultures of streptococcus and other organisms, autogenous vaccines, stock vaccines. Examples include Vancott's vaccine and Inava endocarp vaccine.^[3] The demanding primary role of any periodontal vaccine would be to eradicate the global periodontal disease burden with the ultimate purpose of lowering periodontal disease associated morbidity in humans. The role of any vaccine, however, should also be seen within the context of changes in lifestyle. The vaccine effect should be seen to enhance the feasibility of maintaining oral health and to maximize retention of the natural dentition, thus minimizing the need for prosthetic or implant restorations in the oral cavity. The so-called "healthy gum-healthy body" lifestyle could also lessen the economic burden incurred by restorative dental treatment.^[1,4] Main limitation in the vaccine preparation is the fact that periodontal disease is multifactorial and polymicrobial in origin. Thus, a vaccine targeting only the most probable pathogenic organism may have to be used. Apart from this, efficacy in each individual may not be same due to the variations in the serotypes or genotypes of the organisms among different individuals. Animals differ qualitatively from humans, with respect to the oral microbial ecosystem, the histological components of the periodontal lesions, the nature of immune responses and control over immunoglobulin class and subclass responses. So, results of animal studies may not be directly generalized to humans.^[2,4]

Porphyromonas gingivalis AS A TARGET FOR PERIODONTAL VACCINE

P. gingivalis has been implicated as a major periodonto-pathogen in human periodontitis.^[5] In this context, it has developed a variety of survival strategies enabling it to evade host defence mechanisms. Virulence components of the bacterial cell include cysteine proteases, fimbriae, capsular polysaccharide (CPS), lipopolysaccharide, and outer membrane vesicles.^[6] For active immunization against periodontal disease various target organisms for vaccine preparation have been tried. *P. gingivalis* and *A. actinomycetemcomitans* are of

prime importance owing to their omnipresent role in the pathogenesis of periodontal disease.^[2,6] Gingipains is the specific term used to describe cysteine proteases that impart major pathogenic capability to *P. gingivalis* and can be grouped into: Gingipains R (RgpA and RgpB): cleaves proteins at arginine residues; and 2. Gingipain K (porphypain 2, Kgp): cleaves proteins at lysine residue.² Both RgpA and Kgp (but not RgpB) have a hemagglutinin domain that is essential for the adherence to erythrocytes, while the catalytic domain (in RgpA, RgpB, and Kgp) plays an important role in the evasion of the host defense system by degrading immunoglobulins and complement proteins and by disturbing the functions of neutrophils. Spurred by these findings, an active immunization program using purified *P. gingivalis* cysteine protease (porphypain-2) has been carried out, which resulted in a significantly elevated specific IgG antibody response that suppressed *P. gingivalis*-induced bone loss in *Macaca (M.) fascicularis*.^[1,6] Adherence of bacteria to host tissues is a prerequisite for colonization and also one of the virulence factors of bacteria. Developing monoclonal antibodies against the colonization factor of *P. gingivalis* could also be a potential target for immunotherapy. The two major colonization factors of *P. gingivalis* are coaggregation factor (outer membrane proteins OMPs) & hemagglutinins.^[2,6]

***Aggregatibacter actinomycetemcomitans* AS A TARGET FOR PERIODONTAL VACCINE**

A. actinomycetemcomitans is considered another important pathogen in human periodontal disease, especially in the localized form of aggressive periodontitis.^[1] Harano *et al.* prepared an antiserum against a synthetic fimbrial peptide of *A. actinomycetemcomitans* and found that it blocked the adhesion of the organism to saliva-coated hydroxyapatite beads, to buccal epithelial cells, and to a fibroblast cell line.^[7] Also, subcutaneous and intranasal immunization of mice with capsular serotype b-specific polysaccharide antigen of *A. actinomycetemcomitans* resulted in a specific antibody that efficiently opsonized the organism.^{1,7} Mice immunized with antisurface associated material from *A. actinomycetemcomitans* exhibited a rise in protective antibody levels acting as an opsonin.^[2,8]

PLANTIBODIES

A very recent approach for vaccination strategies is molecular biological techniques to express bacterial or viral antigens in plants, which could be used as orally administered vaccines.^[4] This suggests the potential use of plants in synthesizing adjuvant fimbrial protein for the development of adjuvant mucosal vaccines against *P. gingivalis*. Further studies must be needed to test the efficacy of plantibodies in eliminating periodontopathic bacteria.^[2,8]

CONCLUSION

However, the elimination of the periodontopathogens does not eliminate the periodontal disease as proposed in the ecological plaque hypothesis. It states that any change to the environment induces a response in the micro flora, and vice versa. Implicit in this hypothesis is that, although disease can be treated by targeting the putative pathogens directly. However, long-term prevention will only be achieved by interfering with the underlying changes in the environment that drive the deleterious shifts in the micro flora. Thus, the current status of our understanding in the field of vaccines against periodontal disease is incomplete but extensive research in this direction may hold a promising future in development of periodontal vaccines.

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