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Periodontal vaccine: a new adjunct in periodontal therapy

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ABSTRACT: Periodontal diseases have a multifactorial etiopathogenesis hence a combined intervention strategy, aiming both specific pathogenic species and the host immune response to prevent the initiation and arrest the progression of periodontal disease is needed. Hence the emerging concept of "Periodontal Vaccine" which evokes the host immune response and induce a specific immune resistance to a bacterial or viral infection may have an important adjunctive role in the disease prevention. Studies have reported that combining key gingipain sequences into a chimera vaccine produced an effective therapeutic intervention that protected against P. gingivalis induced periodontitis. Because of the insufficient quantity and quality of animal trials, no adequate evidence could be gathered to use the beneficial effects of these animal experiments to formulate a human periodontal vaccine. Thus, good-quality animal trials are needed in this field of vaccine testing for a combined proteomic genomic immunologic strategy to generate multispecies periodontal vaccine which may be a boon in future in the attempts of periodontal disease prevention.

KEYWORDS: Periodontal vaccine, Chimera vaccine, Gingipains

I. INTRODUCTION

The etiopathogenesis of periodontal disease is a multifactorial model in which host associated immune dysfunction, microbial, genetic, systemic factors and environmental factors have got an evident role to play in the onset and progression of the disease. Thus, there is need for a combined intervention strategy, aiming both specific pathogenic species and the host immune response to prevent the initiation and arrest the progression of periodontal disease. Here in this context the emerging concept of "Periodontal Vaccine" which induce a specific immune resistance to a bacterial or viral infection come to play its role.

Vaccination is induction of immunity by injecting a dead or attenuated form of a pathogen.[1]

It has long been recognized that individuals who recovered from a disease developed subsequent resistance to the same. Vaccination 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.[2]The prime important fact 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]

With the rapid evolution of microbial genome sequencing and bioinformatics, we have the potential to examine all the genes and proteins from any human pathogens. And these advancements have provided us with the new targets for antimicrobial drugs and vaccines. Availability of periodontal vaccine would not only prevent or modulate the course of periodontal disease but also enhance the quality of life of people for whom periodontal treatment cannot be easily obtained.[4]

RATIONALE FOR DEVELOPMENT OF PERIODONTAL VACCINE

- The primary aim of a periodontal vaccine is to eradicate the periodontal disease burden.
- To maintain oral health and optimize the retention of the natural status
- Moreover, recent findings that prevention or treatment of periodontal diseases is a baseline

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step for the effective management of atherosclerosis, uncontrolled diabetes, and low weight pre-term birth or preeclampsia.[5]

NEED FOR A PERIODONTAL VACCINE

1. To fight bacteria which causes host immune response impairment; P. gingivalis produces proteases that degrades serum antibacterial components (antibodies, complement protein) and immune cell derived peptides (eg.Cytokines). A.actinomycetemcomitans produce a protein (leukotoxin) that specially toxic to host immune cells (e.gneutrophiles and monocytes) and also produces factors that can inhibit immune responses.[4]

2. To decrease Periodontal disease incidence

Systemic changes predispose to various conditions (myocardial infarction, cerebrovascular stroke, pneumonia etc). Microbial front can also be there. P.gingivalis antigen heat shock protein is an immunodominant antigen of many microorganisms.HSP-60 has been associated with atherosclerosis and Chlamydia pneumonia infection.[4]

3. Financial

Availability of vaccine for prevention of periodontal disease would be of great benefit in both developing and developed countries.[4]

Periodontal Vaccine: It's Implication In Periodontitis

Researchers have precised the number of putative periodontal pathogens down to six or seven, such as P.gingivalis, T.denticola and T.forsythia, A.a.comitans, P.intermedia and F.nucleatum which are predominantly obtained in sites demonstrating periodontal disease activity.

The target antigens have evolved from the whole organism to specific virulence factors (structural components or secreted products) that could confer immunity against colonization or the virulent activity of putative periodontal pathogens.

A new milestone was achieved when the vaccine research against periodontitis has shifted toward identification of valid antigenic targets/molecules of P. gingivalis and A. actinomycetemcomitans. Periodontal vaccination aims to prevent or modulate the course of periodontal diseases as well as it enhance the quality of life of people for whom periodontal treatment cannot be easily obtained.

P. gingivalis has emerged as the most potential vaccine candidate because this pathogen pathogen carries several high-potent antigens, which are used as subunits for development of active immunization.[6]

TYPES OF PERIODONTAL VACCINATION

Active immunization

- Whole bacterial cells
- Sub unit vaccines
- Synthetic peptides as antigens

Passive immunization

• Murine monoclonal antibody
• Plantibodies

Genetic immunization

- Plasmid vaccines
- Live, viral vector vaccines

Active immunization: Here administration of killed or live attenuated products derived from micro-organisms stimulates the individual immune system.[7] Further subdivided into:

a) Whole bacterial cells eg: P. Gingivalis whole cells.

Klausen B. et al. reported that serum antibodies to whole cells and partially purified fimbriae from P.gingivalis were elevated in rats immunized with P.gingivalis cells.

Also decreased periodontal tissues destruction activities of collagenase and cystein proteinases was noted.[8] Formalin killed whole cells of P.gingivalis vaccine has resulted in blockage of PGE2 response to LPS challenge.[9]

b) Sub unit vaccines e.g. using virulence factors of P.gingivalis such as gingipains.

The role of P. gingivalis as a keystone pathogen in the initiation and progression of chronic periodontitis suggests that a strategy of targeting the major virulence factors of the bacterium, the gingipains by vaccination may have utility in the prevention of P. gingivalis-induced periodontitis.

The two classes of cysteine proteases produced by P.gingivalis known as gingipains which include lysine specific gingipainKgp and the arginine specific gingipainsRgpA and RgpB have been implicated in the pathogenesis of periodontitis. The gingipains modulate the immune system and disrupt immune inflammatory responses potentially leading to increased tissue breakdown.[10] Hence immunization with gingipains prevents colonization with P.gingivalis and reduces bone loss.[11]

Studies using the gingipains as a prophylactic vaccine that induces a high-titre antibody response in naive animals before superinfection with the pathogen have shown protection against alveolar bone resorption.[12]

Also, patients with P. gingivalis-associated periodontitis harbour the pathogen at above threshold levels in subgingival plaque and exhibit an inflammatory immune response, hence it is possible that therapeutic vaccination could exacerbate inflammation and bone resorption in these patients. Here we show that therapeutic vaccination with a chimera antigen targeting the gingipains protects against alveolar bone resorption in P. gingivalis-associated experimental periodontitis and that this protection is mediated via a predominant Th2 anti-inflammatory response with the production of gingipainneutralising IgG1 antibodies.[12]

Adoptive transfer of KAS2-A1-specific IgG1 or IgG2 expressing B cells confirmed that IgG1- mediated protection. Furthermore, parenteral or intraoral administration of KAS2-A1-specific polyclonal antibodies protected against the development of P. gingivalis-induced bone resorption. The KAS2-A1-specific antibodies neutralised the gingipains by inhibiting: proteolytic activity, binding to host cells/proteins and co-aggregation with other periodontal bacteria. Combining key gingipain sequences into a chimera vaccine produced an effective therapeutic intervention that protected against P. gingivalis induced periodontitis.

c) Synthetic peptides eg: fimbrial peptide in the gnotobiotic rat model.

Based on the protein structure of fimbrillin, these synthetic peptides can inhibit the adhesion of P.gingivalis to saliva coated-hydrxyapatite crystals.[13]Hisashi Takiguchi et al, studied the bactericidal activity on P.gingivalis by the IgG1 monoclonal antibody Pg-OMP A2. They determined that Pg-OMP A2 killed P.gingivalis by activating both the classical and alternative complement pathways.

They concluded that Pg-OMP A2 has an in vitro complement-mediated bactericidal activity to P.gingivalis. Pg-OMP A2 may contribute to the development of a local immunotherapy that can be applied in the gingival crevice of a patient with P.gingivalis related periodontitis, or be a vaccine candidate.[14]

PASSIVE IMMUNIZATION:

Here, the antibodies are formed in one individual and are transferred to another. Passive immunization has shown to reduce P.gingivalis colonization and prevent recolonization. Passive immunization can be done by murine monoclonal antibodies: here antibodies are obtained by inoculating antigens into mice and plantibodies-involves molecular biologic techniques to express bacterial or viral antigens in plants which could be used as orally administered vaccines.

GENETIC IMMUNIZATION:

Here, Gene encoding DNA plasmids which are required for antigen production are transferred to an individual. This involves genetic recombination technology. They are of two types:

a) Plasmid vaccines: plasmids are fused with the DNA of a particular pathogen and inoculated in animal for antibody production, however it may cause oncogenesis.
b) Live viral vector vaccines: Variety of infectious but non disease causing DNA or RNA viruses or bacteria is engineered to express the proteins of disease-producing organism.[2]Those vectors enter the body cells, produce proteins and induce humoral or cellular immune response.

HUMAN PERIODONTAL VACCINES

Three types of vaccines are employed for the control of periodontal disease[15]

(i) Pure culture of streptococci and other oral organism.
(ii) Autogenous vaccine
(iii) Stock vaccine such as vancott's vaccine or Inava Endocarps Vaccines.

AUTOGENOUS VACCINE

Plaque samples removed from periodontally diseased site are sterilized by heat or by immersion in iodine or formalin solution and reinjected into same patient either locally or systemically.

STOCK VACCINE

It is prepared from stock microbial stain. A significantly higher level of alveolar bone, strongly implying an immune –modulating role for the cross-reactive peptide number 19 in periodontitis was demonstrated in patients whose sera recognised both P.gingivalis Heat Shock Protein (HSP) peptide number 19 and cross-reactive human HSP peptide number 19.[16,17] Eventhough success has been achieved in the case of animal models, there are several reasons which have to be overcome to make the dream of periodontal vaccine for humans a reality.

Limitations Of Periodontal Vaccine

The complexity of the periodontopathic bacteria might be a problem as a substantial number of bacteria appear to be involved in periodontal disease. So determination of an antigen for the vaccine may pose as a major limitation.

Some more of the serious complications may stem from the vaccine or from the patient. Vaccines may be contaminated with unwanted proteins or toxins, or even live viruses. The patient may be hypersensitive to minute amounts of contaminating proteins, or immuno-compromised, in which case any living vaccine is usually contraindicated.

FUTURE DIRECTIONS

Subunit vaccines have been developed based on viral and bacterial peptides or plasmid vectors. In fact, DNA vaccines that were first described less than five years ago have already progressed to phase I clinical trials in healthy adult humans. They might induce immunity to numerous agents, including periodontopathic bacteria, following confirmation of their safety. DNA vaccines offer several distinct advantages. Firstly, DNA vaccines can be manufactured more easily than vaccines consisting of an attenuated pathogen, an outer or internal protein or a recombinant protein. The second advantage is that since DNA is stable by nature and resistant to extremes of temperature, storage, transport and distribution, it might be highly practical.

The third advantage of vaccination with DNA is the simplicity of changing the sequences encoding antigenic proteins by means of mutagenesis and of adding heterologous epitopes by basic molecular genetics. The immunogenicity of the modified protein may be directly assessed following an injection of DNA vaccine.

DNA vaccination has been studied in animals. Most of the investigated pathogens have been viruses, for instance bovine herpes virus, hepatitis B virus, hepatitis C virus, herpes simplex virus, human immunodeficiency virus-1, influenza virus and lymphocytic choriomeningitis virus.

Some genes from periodontopathic bacteria have been cloned and these genes could be used as a vaccine to protect against periodontitis. DNA vaccines have distinct potential for preventing various infectious diseases, including periodontal disease, in humans.[3]

II. CONCLUSION

Long-term prevention of periodontitis will only be achieved by targeting the underlying host microbial environmental changes. Vaccines targeting the polymicrobial etiology of periodontal disease could act as an important adjunct to mechanical debridement. Hence the concept of combined proteomic genomic immunologic strategy to generate multispecies periodontal vaccine will be a boon in future in the attempts of periodontal disease prevention.

Because of the insufficient quantity and quality of animal trials, no adequate evidence could be gathered to use the beneficial effects of these animal experiments to formulate a prophylactic human periodontal vaccine. Thus, good-quality animal trials are needed in this field of vaccine testing

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