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Periodontal Vaccines: A Sophisticated Treatment Design in the Future?

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ABSTRACT

Periodontal vaccine is a boon in periodontics. 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. In late eighteenth century, Edward Jenner developed and established the principle of vaccination using the cross protection conferred by cowpox virus, which is non pathogenic in humans. Vaccination accomplished can be active immunization, passive immunization or DNA vaccination, made from the antigenic epitopes in periodontopathic bacteria. The objective of periodontal vaccine is to identify the antigens involved in the destructive process of periodontitis against which antibodies would be evoked to exert protection. It also aims to induce mucosal antibody response with little or moderate doses of vaccine. Ongoing research & collaborative efforts can result in development of functional periodontal vaccine for human use in future.

Key words: Vaccines, Active immunization, Passive immunization, DNA vaccination, Epitope.

INTRODUCTION

It is now thought that periodontal disease is a specifically combined infection of polymicrobial Gram-negative anaerobic bacteria, including Porphyromonas. gingivalis, Treponema denticola and Tunnerella forsythia, and Aggregatibactor actinomycetemcomitans, all of which have been proposed as predominant pathogens, exclusively or synergistically with other bacteria, including Prevotella intermedia, Campylobacter rectus, Fusobacterium nucleatum and herpes virus.

Vaccination is induction of immunity by injecting a dead or attenuated form of pathogen.[1] 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.[2]

Concepts behind periodontal vaccines

Periodontal disease is a polymicrobial infection. The second is that it is a major cause of adult tooth loss worldwide. Systemic sequalae to periodontitis like atherosclerosis, diabetes mellitus, pre-term low-weight birth, rheumatoid arthritis, etc., is of at most importance and drives to the ultimate purpose of lowering periodontal disease associated morbidity in humans. Despite the considerable numbers of cultivable microorganisms identifiable in the subgingival niche, researchers have narrowed the number of putative periodontal pathogens down to six or seven, *P. gingivalis*, T.

denticola and *T. forsythia*, A. actinomycetem-comitans, *P. intermedia, C. rectus*, and *F. nucleatum,* which are predominantly cultivated in sites demonstrating disease activity and Most immunization approaches, both active and passive, against periodontitis have been focused on P. gingivalis and A.actinomycetemcomitans.[3]

The types of periodontal immunization can be active or passive. Active immunization includes whole bacterial cells, Sub unit vaccines and Synthetic peptides as antigens where as Passive immunization includes murine monoclonal antibody and plantibodies

Active immunization

Periodontal vaccines against *P.gingivalis*

P. gingivalis has emerged as the leading candidate pathogen in the development of chronic periodontitis. It is a gram-negative, non-spore/ forming, nonmotile, assacharolytic, obligate anaerobic coccobacillus.[4] The virulence factors of P. gingivalis which have been used as subunits for the development of active immunization are: outer membrane proteins, gingipains, fimbriae and heat shock protein.[5]

Whole cell as antigen

This was one of the first approaches tried in various animalmodels. In preliminary studies, *Persson et al* reported that active immunization of nonhuman primate, Macaca fascicularis, with killed P. gingivalis whole cell conjugated with syntex adjuvant formulation inhibits the progression of periodontal tissue destruction.[6] *Page RC* used ligature-induced periodontitis in the nonhuman primate Macaca fascicularis as a model, 10 animals were immunised using intact killed *P. gingivalis* and SAFM adjuvant and 10 controls using adjuvant only.[7] However, active immunization with whole cells might induce exaggerated inflammatory responses in the host. Bone density was significantly decreased in ligated teeth from nonhuman primates immunized with whole-cell antigens of *P.gingivalis* and *P.intermedia*.[8]

Gingipains as antigens

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 and gingipain K.

Hemagglutinin domain and Catalytic domain are the two types of domains are present in gingipains. Gingipains vaccines are mainly DNA vaccines.DNA vaccines induce both humoral and cellular immunity.[9] 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.[10]

Rats immunized with rHA2 immunogen developed significantly higher IgG response levels and a relatively lower Th2/Th 1- driven response, which gave some clinical protection from periodontitis.[11]

Fimbriae as antigens

Fimbriae from P.gingivalis play an important role in adhesion to oral tissues and are also highly immunogenic.[12] *O'Brien- Simpson et al*. reported that the, incidence of secondary lesions was reduced by immunization with lithium diiodosalicylate extracts of membranes from P.gingivalis in the mouse abscess model but tissue invasion was not elicited. They also demonstrated that immunization with a purified 75-kDa outer membrane protein reduces the activities of collagenase, gelatinase and cysteine proteases in gingival tissue. However, it did not prevent periodontal boneloss.[13] The fimbriae of P. gingivalis, which consist of one major fimbriae and two minor fimbriae of 67 kDa and 72 kDa, respectively, are virulence factors in the pathogenesis of periodontal disease. When rats were parenteraly immunized with purified 43-kDa fimbrial protein, the resultant fimbrial A-specific antibodies in serum and saliva gave a satisfactory level of protection against P. gingivalis-induced alveolar bone loss.[14]

Synthetic peptides as antigens

These require synthesis of linear and branched polymers of 3-10 amino acids based on known sequence of microbial antigens. Such peptides are weakly immunogenic by themselves and need to be coupled to large proteins to induce antibody response. Synthetic peptide based on the protein structure of fimbrillin inhibit the adhesion of *P.gingivalis* to saliva coated hydroxyapatite crystals.[2]

Small antigenic peptides are normally poorly immunogenic, and it is therefore necessary for small peptides to be added a carrier molecule for inducing an immune response. Recombinant P. gingivalis HSP60 was produced and purified from P. gingivalis GroEL gene.[15]

Passive immunization

Passive immunization against *P. gingivalis*

Antigens are injected into vector that produce antibodies. These antibodies when inoculated into host bring about passive immunization. *Hisashi Takiguchi et al*, developed a panel of monoclonal antibodies by immunizing mice with purified r 40-kDa OMP.[16] They concluded that Pg-OMP A2 has an in vitro complement-mediated bactericidal activity to P.gingivalis. Outer membrane proteins (OMPs) are important coaggregation factors and as such are major colonization factors of P. gingivalis. Since IgG specific for the 40 kDa-OMP inhibited coaggregation of P. gingivalis vesicles and S. gordonii, it could conceivably be used to prevent *P. gingivalis* infection.[17]

Local passive immunization with rabbit antiserum against P. gingivalis hemagglutinin has infact resulted in a reduced colonization by exogenous P. gingivalis in the subgingival area over a 3-week period.[18] A cDNA fragment of P. gingivalis major fimbrial protein (fimA) was cloned into a plant expression vector. When this chimeric plasmid was transferred into potato (Solanum tuberosum) cells, the ctb-fimA cDNA fragment was detectable in its genome.[19] Thus monoclonal antibody specific to a bacterial antigen could prove to be an effective mode of passive immunization against P. gingivalis and possibly other periodontopathic bacteria.

Periodontal vaccines against A. actinomycetem-comitans

A. actinomycetemcomitans is considered an important pathogen in human periodontal disease, especially in aggressive periodontitis. A synthetic oligopeptide was prepared based on the aminoacid sequence of A. actinomycetemcomitans fimbriae which was found to be effective in rabbit model, ensuring inhibition of adhesion and its subsequent colonization.[20]

When mice were immunized with anti surface associated material from A. actinomycetemcomitans, it yielded a raised protective opsonic antibody response and rapid healing of the primary lesions following a challenge with live A. actinomycetemcomitans.[21]

Limitations

a) Multi factorial and complex nature of periodontal disease.
b) Maintaning adequate antibody levels for longer periods.
c) Vaccine contamination.
d) To stimulate helper T-cell polarization that exerts cytokine functions optimal for protection against bacteria and tissue destruction.
e) Toxic reactions to inactivated whole vaccines.[3]

Future of periodontal vaccines

Periodontal vaccine trials aim to stimulate the immune system to produce increased levels of immunoglobulin of desired specificity immunization of dendritic cells pulsed with antigens, the use of improved adjuvant formulas (e.g. the use of alum as an alternative to HSP-based adjuvant), the use of recombinant plant monoclonal antibodies (plantibodies) and the use of transgenic microorganisms as antigen vectors.[19,22]

DNA vaccines offer several distinct advantages like

a) Can be manufactured more easily
b) DNA is stable by nature
c) simplicity of changing the sequences encoding antigenic proteins
d) The immunogenicity of the modified protein may be directly assessed following an injection of DNA vaccine.

A vaccine incorporating the poly-reactive monoclonal antibody recognized peptide number 19 of 37 synthetic peptides spanning the whole molecule of P. gingivalis HSP60 might be useful in multi factorial diseases such as atherosclerosis and diabetes supporting the role of molecular mimicry in the periodontal-atherosclerosis link.[23]

A genetically engineered mouse system developed recently may prove useful for the study of periodontal disease

CONCLUSION

To prevent colonization of periopathogens, vaccination may be an important adjunctive therapy to mechanical debridement in humans, but extensive research in this direction may hold a promising future in development of periodontal vaccines. A sophisticated vaccine design regimen targeting multiple pathogenic species is definitely needed against periodontitis and periodontitis induced systemic diseases.

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