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Periodontal Vaccine: Review article

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Abstract
With the rapid growth of microbial genome sequencing and bioinformatics analysis tools, we have the potential to examine all the genes and proteins from any human pathogen Recent advances in cellular and molecular biology have led to the development of new strategies for vaccines against many types of infectious diseases. It has long been recognized that individuals who recovered from a disease developed subsequent resistance to the same. In the 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 may be an important adjunctive therapy to mechanical debridement in near future. Its not a myth but a reality which will come true in the near future if research is carried out in right way in right direction.

Keywords: microbial genome, vaccination, periodontal disease

Introduction
Recent advances in cellular and molecular biology have led to the development of new strategies for vaccines against many types of infectious diseases. It has long been recognized that individuals who recovered from a disease developed subsequent resistance to the same [1].
In the 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.
With the rapid growth of microbial genome sequencing and bioinformatics analysis tools, we have the potential to examine all the genes and proteins from any human pathogen. This technique has the capability to provide us with new targets for anti-microbial drugs and vaccines. However, to realize this, potential new bioinformatics and experimental approaches for the selection of these targets from the myriad of available candidates are required [2].
Vaccination is a process that induces specific immune resistance to a bacterial or viral infection.
Chronic inflammation, if protracted, can result in an adaptation called the specific immune response. The specific immune response requires lymphocytes that use two types of receptors to generate specific immune responses, the b-cell antigen receptor and the t- cell antigen receptor [3].

Four phases are involved in the generation of specific immunity [2].
- **Clonal selection:** Selection of lymphocytes that bear receptors recognizing the specific antigen
- **Clonal expansion:** Proliferation of those lymphocytes
- **Clonal contraction:** Death of effector lymphocytes
- **Memory:** Maintenance of an expanded clone of cells that bear the specific receptors recognizing the antigen.

As long as a sufficient number of lymphocytes are maintained to provide protection against a specific pathogen, the individual is said to be immune.
"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."

Types of vaccination [4]
Active immunization: Here, an individual immune system is stimulated by administrating killed or live attenuated products derived from micro-organisms.
Passive immunization: Here, the antibodies formed in one individual are transferred to another.
DNA vaccination: Here, DNA plasmids encoding genes required for antigen production are transferred to an individual.

Characteristics of an effective vaccine [5]
- Safety
- Protectivity
- The ability to provide sustained protection
- The ability to produce neutralizing antibodies
- Stimulation of protective t-cells.

Practical considerations [3]
- Cost-effectiveness
- Biological stability
- Access
- Minimum contraindications and side effects

Pathogenesis of periodontitis [6]
Periodontitis is a disease of multifactorial origin with interaction among host, micro-organisms and environmental factors which includes genetic factors as well.

Over 300 species of micro-organisms have been found to colonize the periodontal tissues, of which the following are considered to be the primary pathogens causing periodontitis:

- Porphyromonas gingivalis
- Agregatibacter actinomycetemcomitans
- Tannerelaforsythensis

These bacteria produce an array of antigens that stimulate - pro- inflammatory cells and leads to the production of a wide variety of cytokines. These antigens may stimulate Th1 or Th2 cells.

Antigens are taken up by dendritic cells and presented to CD-8 or CD-4 cells along with MHC antigens.

CD-8 cells → Th 1 response → CMI → Pro inflammatory

CD-4 cells → Th 2 response → Ab response → Protective

The host produces anti bacterial substances such as defensins, cathelicidins and saposins, which protect the host tissues from bacterial products and forms the first line of defense. However, sometimes these are inactivated by the bacterial virulence factors. Once bacteria break this barrier, cytokines are produced, which can be both proinflammatory and anti-inflammatory. Production of inappropriate cytokines results in periodontitis [7].

Indication for periodontal immunotherapy [7]

- Severe periodontal disease with loss of bone around teeth
- Inflammation and association with oral bacterial infection below gum line
- Exacerbated diabetes and CVD
- Where mouth rinses don't work

History of periodontal vaccines [8]

In the early twentieth century, three periodontal vaccines were employed:

- Pure cultures of streptococcus and other organisms
- Autogenous vaccines
- Stock vaccines

Examples include Vancott's vaccine and Inava endocarp vaccine.

The search for the etiologic agents of periodontal disease and the vaccines ended inconclusively; probably the most important reason for the failure was the inability to conduct adequately controlled clinical trials and experiments.

Autogenous Vaccine [9]

- These are prepared from dental plaque samples of patients with destructive periodontal diseases. Plaque samples are removed from the diseased site. They are sterilized by heat or by immersion iniodine or formalin solution and reinjected into the same patient either locally at the site or systemically.

Mechanism of action

Types of periodontal immunization

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 [10]

Whole cells

- Here, the entire cell with its components is inoculated into a host to bring about active immunization. Klausen; 1991 have shown that levels of serum antibodies to both whole cells and partially purified fimbriae from *P. gingivalis* were elevated in rats immunized with *P. gingivalis* cells and that the activities of collagenase and cysteine proteinases in gingival and periodontal tissues were decreased.
- Kesavalu; 1992 observed protection against invasion, but no colonization against *P. gingivalis* in a mouse chamber model by immunization with either killed heterologous invasive or non-invasive *P. gingivalis* strains. The immune response to whole cells or selected envelope component did not completely abrogate lesions, but eliminated mortality.

Active immunization with whole cells might induce exaggerated inflammatory responses in the host. It was found that bone density was significantly decreased in ligated teeth with nonhuman primates immunized with whole cell antigens of *P. gingivalis*.

Outer components [11]

In this type, a part of the bacterial cell is used for immunization. Either the outer component or the fimbriae is used.

Fimbriae from *P. gingivalis* play an important role in adhesion to oral tissues and are highly immunogenic.

- Evans; 1992 reported that immunization with highly purified *P. gingivalis*fimbrial preparations as well as whole cells and soluble antigens of *P. gingivalis* protected against periodontal destruction induced by *P. gingivalis* in gnotobiotic rats. They suggested that fimbrial protein might serve as a model of effective vaccines against periodontitis.
- Bird; 1995 showed that immunization of experimental animals with an outer membrane preparation isolated from *P. gingivalis* induces elevated levels of specific antibody and provides protection against the progression of periodontal disease.
- Chen; 1995 demonstrated that immunization with a purified outer membrane protein reduces the activities of collagenase, gelatinase and cysteine proteases in gingival

tissues. However, it did not prevent periodontal bone loss.

Outer membrane protein [12]

- It was seen that transcutaneous injection of outer membrane protein (OMP) inhibits co-aggregation of *P. gingivalis* with *Streptococcus gordonii*.
- This also can be used for vaccine development for passive immunization. Polyclonal anti-40 kDa OMP antibody exhibited potentially protective, complement-mediated bactericidal effect. (Katoh *et al* 2000).
- Chen; 1995 demonstrated that immunization with a purified outer membrane protein reduces the activities of collagenase, gelatinase and cysteine proteases in gingival tissues. However, it did not prevent periodontal bone loss.

Gingipains [13]

These are cysteine proteinases which cleave synthetic and natural substrates after arginine or lysine residues and are referred to as arginine gingipain (Rgp) and lysine gingipain (Kgp).

Rgp and Kgp are key determinants in the growth and virulence of *P. gingivalis*.

Therefore, it is likely that virulence of *P. gingivalis* can be attenuated by inactivation of Rgp and Kgp with proteinase inhibitors of antibodies specific to Rgp and Kgp.

- Genco*et al.*, showed that immunization of mice with a peptide derived from the amino terminal sequence of catalytic domains of gingipains resulted in protection from *P. gingivalis* invasion.
- Gibson *et al.*, showed that immunization with Rgp A stimulates the production of hemagglutinin domain specific antibodies which contribute to the prevention of *P. gingivalis* mediated bone loss.

Heat shock protein [14]

- Heat shock proteins have an important role in inflammatory mechanism, autoimmune disease and atherosclerosis. Homologues of specific stress protein families have been demonstrated to be present in oral bacteria including *Fusobacteriumnucleatum, Prevotellaintermedia, Prevotellamelaninogenica, A.a*and *P. gingivalis*.
- Rats immunized with *P. gingivalis* HSP60 showed decrease in bone loss induced by infection with multiple periodontopathic bacteria.
- Significant association between HSP90 concentration and microbial colonization has been observed.

Hemagglutinins[3]

Non-fimbrial adhesion hemagglutinin B (HagB) is a potential vaccine candidate.

Hemagglutinin mediates bacterial attachment and penetration into the host cells, as well as agglutinates and lyses erythrocytes to intake heme, an absolute requirement for growth.

Rats immunized subcutaneously with recombinant HagB were protected against periodontal bone loss induced by P. gingivalis strain ATCC 33277. Such treatments significantly decrease recolonization of P. gingivalis for up to 9 months. (Kaizuka 2003).

Synthetic peptides [7]

These require synthesis of linear and branched polymers of 3-10 amino acids based on the known sequences of microbial antigens. Such peptides are weakly immunogenic by themselves and need to be coupled to large proteins to induce antibody response.

Two ways of developing synthetic peptide vaccines are as follows:

- By deduction of the protein sequence of microbial antigens from RNA sequence data.
- By testing overlapping peptides and by mutational analysis.

Advantages of synthetic peptide are

- Safe
- Cheap
- Easy to store and handle
- Ideally suited for specific targeting, which is not possible with classical vaccines.

Genco; 1992 found that synthetic peptides based on the protein structure of fimbrillin inhibit the adhesion of Pg to saliva-coated hydroxyapetite crystals *in vitro*.

Lee & coworkers 2006

- Recombinant P. gingivalis HSP60 was produced and purified from P. gingivalisGroEL gene. Rats were immunized with P. gingivalis HSP60, and experimental alveolar bone loss was induced by infection with multiple periodontopathogenic bacteria. There was a very strong inverse relationship between postimmune anti-P. Gingivalis HSP immunoglobulin G (IgG) levels and the amount of alveolar bone loss induced by either P. gingivalis or multiple bacterial infection. Polymerase chain reaction data indicated that the vaccine successfully eradicated multiple pathogenic species [2].

Passive immunization [11]

Passive immunization is short lived, because the host does not respond to the immunization and protection lasts only as long as the injected antibody persists.

Here, the antigens are injected into a vector that produces antibodies. These antibodies, when inoculated into a host, bring about passive immunization. Passive immunization can be brought about in two ways:

- Murine monoclonal antibodies
- Platibodies

Murine monoclonal antibodies [12]

In this, the antibodies are obtained by inoculating the antigens into mice. These antigens are then injected into the host that brings about passive immunization. Booth; 1996 developed a murine monoclonal antibody to *P. gingivalis* that prevented recolonization of deep pockets by this pathogen in periodontitis patients.

- Hisashi *et al*, developed a panel of monoclonal antibodies by immunizing mice with purified r 40-kDa OMP (2000). The objective of their study was to determine the bactericidal activity on P.gingivalis by the IgG1 monoclonal antibody Pg-OMP A2. The results showed

that in the presence of complement, Pg-OMP A2 was lethal to P.gingivalis strains. 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 as a vaccine.

Plantibodies [13]

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.

Advantages

- Higher stability
- Higher degree of functionality and
- Protection against colonization by S mutans.

Genetic immunization [14]

By the early 1990's, scientists had begun to study new approaches for the production of vaccines that differ in structure from traditional ones. The strategy involves genetic engineering or recombinant DNA technology.

There are two types

- Plasmid vaccines
- Live, viral vector vaccines

Plasmid vaccines[4]

DNA does not have the ability to grow, whereas plasmids have the ability to grow. With this ability of the plasmids, they are fused with the DNA of a particular pathogen of interest and inoculated in an animal for the production of antibodies. This is then transferred to the host for immunization.

Disadvantages of plasmid vaccines are that, in some cases it may lead to oncogenesis.

Live, viral vector vaccines [10]

A variety of infectious but nondisease causing DNA or RNA viruses or bacteria have been engineered to express the proteins of a disease-producing organism. The vector enters the body cells where the proteins are generated and then induce humoral or cellular immune responses.

Methods of DNA vaccine administration [12]

- Intranasal
- Intramuscular
- Gene gun

Advantages of DNA vaccines

- The ease of manufacture
- Stable by nature
- Simple

Advantages of periodontal immunotherapy

- Current management options inadequate for many
- Current disease prevention options inadequate for most
- Nonexistence of equivalent technology for periodontal disease control or prevention.

Hurdles in development of vaccine

Periodontal disease is a multifactorial disease. Hence, elimination of certain bacteria may not prevent the onset and progression of the disease. Problems such as maintaining adequate levels of antibodies for long enough, generating T-cell mediated response, multiple antigenicities of various microorganisms remain to overcome. The few similarities between the conventional animal models and human beings, and incidence of toxic reactions to inactivated whole cell vaccines add to our difficulties [10, 12, 13].

Conclusion

The current treatment of periodontitis is nonspecific and is centered on the removal of plaque by mechanical debridement, often involving surgical procedures. This ongoing therapy is costly, painful and has a variable prognosis due in part to poor patient compliance.

The use of antibiotics is limited by the need for constant treatment to prevent re-establishment of the pathogen. The elucidation of specific bacterial etiology suggests that the development of a specific treatment modality to target site colonization is now a rational approach to treat the disease. Vaccination may be an important adjunctive therapy to mechanical debridement in near future. Its not a myth but a reality which will come true in the near future if research is carried out in right way in right direction.

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