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Review Article

Periodontal Vaccine – A Review

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ABSTRACT:
Vaccination is a process that induces specific immune resistance to a bacterial or viral infection. 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 to select these targets from the myriad of available candidates are required.

Key words: Immune response, periodontal vaccine, periodontitis.

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INTRODUCTION

Periodontal diseases belong to a heterogeneous family of diseases, which demands a clear need for a betterunderstanding of the etiology and pathogenesis behind formulation of a vaccine against the same. Both specific and nonspecific plaque hypothesis has its own merits and demerits(1,2).

Extensive research hasbeen conducted to determine the role of cell-mediated immunity and serum antibodies in protection against infectiousagents, less is known about the role of mucosal immunity(3).

Vaccination is a process that induces specific immune resistance to a bacterial or viral infection.

SPECIFIC IMMUNE RESPONSE

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.

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.

"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

Active immunization [3]: Here, an individualimmune system is stimulated by administratingkilled or live attenuated products derived frommicro-organisms.

Passive immunization [Figure 1]: Here, theantibodies formed in one individual aretransferred to another.

DNA vaccination [Figure 2]: Here, DNAplasmids encoding genes required for antigenproduction are transferred to an individual.

Characteristics of an effective vaccine

•Safety
•Protectivity
•The ability to provide sustained protection
•The ability to produce neutralizing antibodies
•Stimulation of protective t-cells.

Practical considerations like
•Cost-effectiveness
•Biological stability
•Access
•Minimum contraindications and side effects

PATHOGENESIS OF PERIODONTITIS

Periodontitis is a disease of multifactorial origin withinteraction among host, micro-organisms and environmentalfactors which includes genetic factors as well.Over 300 species of micro-organisms have been found tocolonize the periodontal tissues, of which the followingare considered to be the primary pathogens causingperiodontitis[4-6]
•Porphyromonas gingivalis
•Agregatibacter actinomycetemcomitans
•Tannerela forsythensis

These bacteria produce an array of antigens that stimulatepro-inflammatory cells and leads to the production of a widevariety of cytokines. These antigens may stimulate Th1 orTh2 cells.
Antigens are taken up by dendritic cells and presented to CD-8or CD-4 cells along with MHC antigens.[7]

CD-8 cells → Th 1 response → CMI → Pro inflammatoryCD-4 cells → Th 2 response → Ab response → Protective
The host produces anti-bacterial substances such as defensins, cathelicidins and saposins, which protect the host tissuesfrom bacterial products and forms the first line of defense. However, sometimes these are inactivated by thebacterial 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]

History of periodontal vaccines

From the time of Edward Jenner's discovery of small pox vaccine in 1796, antigens of infectious pathogenic bacteria and viruses have been the targets for a variety of vaccines against a number of infectious diseases. Thus, most vaccines target one or multiple antigenic components of mono- infecting bacteria or viruses. The principle of vaccination is based on two key elements of adaptive immunity namely specificity and memory.[3]
Three periodontal vaccines were employed 1870Locuis Pasteur creates 1st Live att. Bacterial vaccine(chicpenchoecra)
1885 Pasteur creates the first Live attenuated viral vaccine (rabies) ,1886 Typhoid , 1900 Cholera, 1992 Hepatitis A , 1999 Meningococcal C Conjugate, 2004DTap/IPV DTa/IPV/HibTa/IPV, 2006 (Combine Hib)**(Kudyar, et al.: Periodontal vaccine**) .

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

Here, the entire cell with its components is inoculated into ahost to bring about active immunization.
•Klausen; 1991[8] have shown that levels of serum antibodiesto 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 andcysteine proteinases in gingival and periodontal tissueswere decreased.
•Kesavalu; 1992[9] observed protection against invasion, butno colonization against *P. gingivalis* in a mouse chamber model by immunization with either killed heterologousinvasive or non-invasive *P. gingivalis* strains. The immuneresponse to whole cells or selected envelope componentdid not completely abrogate lesions, but eliminated mortality.

Passive immunization

Passive immunization is short lived, because the host does notrespond to the immunization and protection lasts only as longas the injected antibody persists.Here, the antigens are injected into a vector that producesantibodies.
These antibodies, when inoculated into a host,bring about passive immunization. Passive immunization canbe brought about in two ways:
• Murine monoclonal antibodies
•Platibodies

Genetic immunization

By the early 1990's, scientists had begun to study newapproaches for the production of vaccines that differ instructure from traditional ones. The strategy involves genetic-engineering or recombinant DNA technology.
There are two types:
• Plasmid vaccines
• Live, viral vector vaccines

Preparations of human Periodontal Vaccine

Three types of vaccines were employed for the control ofperiodontal diseases.[31]
These include the vaccines prepared from:
• Pure cultures of streptococci and other oralorganisms
•Autogenous vaccines, which are prepared fromdental plaque samples of patients with destructiveperiodontal diseases. Plaque samples are removedfrom the diseased site and are sterilized by heat or by immersion in

iodine/formalin and are re-injectedinto the same patient, either locally or systemically.
•Stock vaccines such as Van Cott's vaccine, Goldenberg's vaccine, or Inava Endocorps vaccine.

Components of periodontal bacteria tested forantigenicity and potential as vaccine candidates

Generic name	Species name	Antigenic components
Porphyromonas	Intermedia	Whole cell non invasive 381 6235.2 (monkey isolate)
Porphyromonas	Macacae	Whole cell
Treponema	Denticola	Whole cell ATCC 35404
Fusobacterium	Nucleatum	Whole cell ATCC 25586
Actinobacillus	Actinomycete-mcomitans	Formalinized whole cell leucotoxin
Actinomyces	Viscosus	Fimbrial adhesins of T14V

Limitations of periodontal vaccines
However, several issues should be addressed pertinentto the development of a sophisticated vaccine againsthuman periodontitis. Firstly, human periodontal disease is multifactorial caused by manifold pathogens. The intricacy of the periodontopathic bacteria might be a problem asa substantial number of bacteria appears to be involvedin periodontal disease. The multiplicity of pathogenicorganisms indicates that vaccine design against periodontitisis very complex.
Secondly, bacterial whole cells or crudeextracts preparation for vaccination is not desirable becausethe antigenic determinants of bacteria potentially possess a high risk of cross reactivity with human counterparts.
Some more serious complication may stem from the vaccineor from the patient. Vaccines may be contaminated with unwanted proteins or toxins, or even live viruses. Supposedlykilled vaccines may not have been properly killed; attenuatedvaccines may revert to the wild type[3] The patient maybe hypersensitive to minute amounts of contaminating proteins, or immune-compromised, in which case any livingvaccine is usually contraindicated.
Furthermore, importantly, animal models for vaccine trialsmay pose inconsistencies with human models in majorhistocompatibility complex- restriction of antigens presentedby antigen presenting, thus obscuring the immunodominant epitope(s).
A humanized mouse system has been projectedthat has been reconstituted with human peripheral bloodlymphocytes. This system needs to meet the requirement ofleast leakiness of a mouse immune system. More recently, agenetically engineered mouse system, such as the non- obese diabetes Non obese diabetic mouse CB 17- colony of BALB(mouse strain used in the study) prkdcscid/J mouse, has been initiated into the study of infectious and autoimmune diseases in humans. This model may also prove to be avaluable tool for the study of periodontal disease and putativeperiodontal vaccines.[1]
As an innovative strategy, vaccines using cross reactive immunodominant epitopes as antigenic molecules inan attempt to stimulate antigen specific regulatory T-cells (Tregs, CD4+, CD25+, FoxP3+), secreting IL-10 and Transforming growth factor β, may provide new clues for periodontal disease prevention, through the induction of either immune tolerance or an effector function.[45]
Recently, a variety of strategies to enhance theimmunogenicity of antigenic components of B or T lymphocytes have been adopted in vaccine trials againstperiodontal disease. These include, but not limited to, immunization of dendritic cells pulsed with antigens, the use of improved adjuvant formulas (e.g., the use ofalum as an alternative to heat shock protein (Heat shock protein) based adjuvant), the use of recombinant plant monoclonal antibodies (plantibodies),[41,46,47] and the use of transgenic microorganisms as antigen vectors.[48,49] Theseefforts leave challenging areas to be chased further in the search for a more refined design that may guarantee the efficiency and safety of extended immune memory.

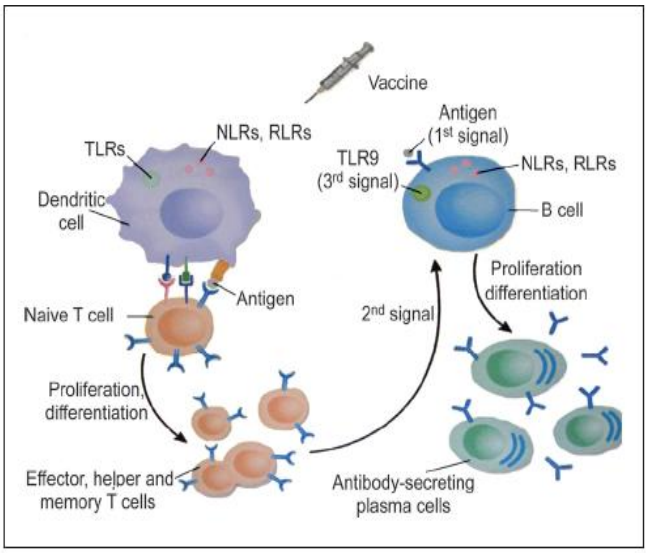
Future of periodontal vaccine-
As yet, there are no periodontal vaccine trials that have been successful in satisfying all requirements; to prevent the colonization of multiple pathogen biofilm in the subgingival area, to elicit a high level of effector molecules such as immunoglobulin sufficient to opsonize and phagocytose the invading organisms, to suppress alveolar bone loss, and to stimulate helper T-cell polarization that exerts cytokine functions optimal for protection against bacteria and tissue destruction.
As an innovative strategy, vaccines using cross-reactive immunodominant epitopes as antigenic molecules in an attempt to stimulate antigen-specific regulatory T-cells (Tregs, CD4+, CD25+, FoxP3+), secreting IL-10 and TGF-β, may provide new clues for periodontal disease prevention, through the induction of either immune tolerance or an effector function.
Periodontal disease as a multifactorial and polymicrobial disease requires a sophisticated vaccine design regimen targeting multiple pathogenic species. Vaccine regimens including the commonly shared antigens by selected periodonto pathogenic species would be considered an innovative strategy.
Traditional periodontal vaccine trials aim to stimulate the immune system to produce increased levels of immunoglobulin of desired specificity. To accomplish this end, a conjugate vaccine (i.e. protein-CPS conjugate), dendritic-cell based immunotherapy, and subunit DNA vaccine encoding the desired immunogenic epitope have been devised.
Animal models for vaccine trials may pose discrepancies with human models in major histocompatibility complex-

restriction of antigens presented by antigen presenting, thus obscuring the immunodominant epitope(s). A humanized mouse system has been proposed that has been reconstituted with human PBLs. This system needs to meet the requirement of least leakiness of a mouse immune system. More recently, a genetically engineered mouse system, such as the NOD.CB17-prkdc^{scid}/J mouse, has been introduced for the study of infectious and autoimmune diseases in humans. This model may also prove useful for the study of periodontal disease and putative periodontal vaccines.

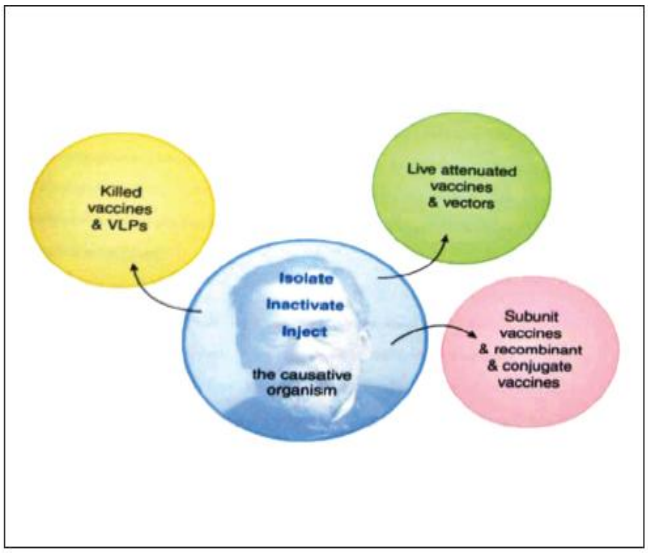
CONCLUSION-

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 iscostly, painful and has a variable prognosis due in part to poorpatient compliance.

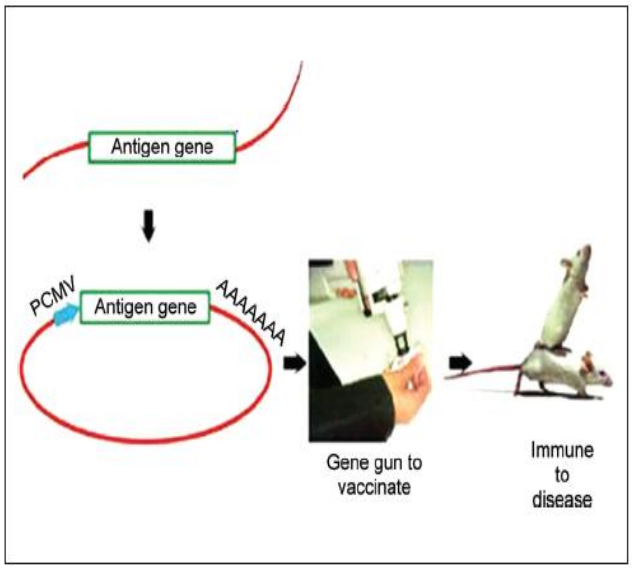
The use of antibiotics is limited by the need for constant treatment to prevent re-establishment of the pathogen. The elucidation of specific bacterial etiology suggests that thedevelopment of a specific treatment modality to target site colonization is now a rational approach to treat the disease. Vaccination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



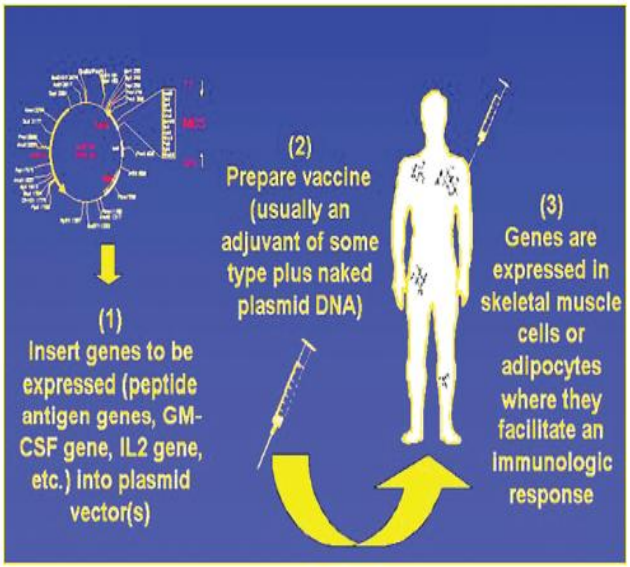
Mechanism of action



Active immunization



Genetic immunization



DNA vaccines

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