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Periodontal Vaccine

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Abstract

The vaccine is the name applied generally to a substance of the nature of dead or attenuated living infectious material introduced into the body. Vaccines are usually prophylactic, i.e. they alleviate the effects of future infection. One such vaccine considered here is the “Periodontal vaccine”. The infectious aetiology of periodontitis is complex. This disease created an interest in finding a solution in the form of vaccines due to its high prevalence rate. Best known is the vaccination and the most crucial application of immunological principles to human health. Number of periodontopathic bacteria decreases by immunization using vaccine against periodontitis. The foremost step in vaccine development is the identification of an antigenic component from various organisms that can provide immune protection. Periodontal vaccine availability would not only prevent and modulate periodontal disease but also enhance the quality of life of people for whom cannot quickly obtain treatment. This review article presents in detail about the periodontal vaccine.

Introduction

Periodontal disease is the processes of peri-tooth structures destruction that support the teeth. These are composed of the gingiva, the periodontal ligament, the cementum, and the alveolar bone. Eventual loss of teeth and partial or full edentulism takes place due to chronic destruction of these supporting structures. 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]

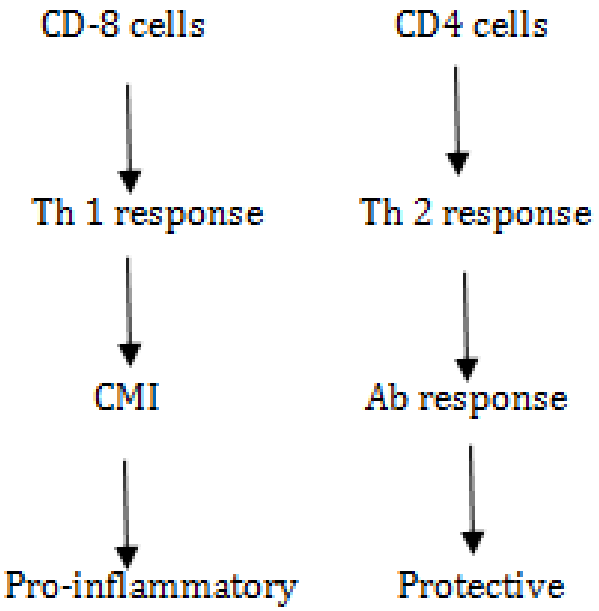
The age-old and time-tested proverb ‘‘Prevention is better than cure’’ sums up the essence of vaccination.[2] Johnson and Curtis, in their excellent review on ‘‘Preventive therapy for periodontal diseases,’’ raised the issue of vaccination against periodontal disease. They noted that vaccine research in periodontal diseases is still in its infancy, and a rational strategy would be first to identify critical pathogens and their virulent strains and virulence factors.[3]

Traditional concepts of the aetiology and periodontal disease initiation stem from the observation that gingival inflammation shows that from the sequential and quantitative microbial load accumulating in the gingival sulcus as an organized biofilm known as bacterial plaque. Research findings on the polymicrobial nature of associated biofilm emerges current concepts. This has led to the notion that biofilm quality is the critical factor in the pathogenesis of the periodontitis. In fact 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, C. rectus, F. nucleatum, and herpes virus.[4]

Many of these may be present in healthy periodontal individuals and can live in commensal harmony with host. Thus, disease episodes may arise from a shift in the ecological balance between bacterial and host factors, as a result of, alteration in the absolute.[5]

It also contributes to the perpetuation of systemic diseases of critical importance (atherosclerosis, diabetes mellitus, etc.). Periodontal vaccine development to alleviate the disease burden may influence these three emerging concepts of periodontal disease.[5]

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. Dendritic cells takes antigens and presented to CD-8 or CD-4 cells along with MHC antigens.



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

Indication for periodontal immunotherapy

- Loss of bone around teeth in severe periodontal disease.
- Association and inflammation with oral bacterial infection below the gum line
- Exacerbated diabetes and CVD
- Where mouth rinses don’t work.[6]

Principles of Vaccination

The vaccination principle is based on two key elements of adaptive immunity, namely specificity and memory. The antigens of vaccine induce clonal expansion in specific B and T cells, leaving behind memory cells population. The next encounter is enabled with the same antigens to generate a secondary response which is more rapid and effective than the standard primary response. The aim in vaccine development is to alter a pathogen or its toxins in such a way that they become innocuous without losing antigenicity. This is possible because antibodies and T cells recognize particular parts of antigens, the epitopes, and not the whole organism or toxins.[5]

Key features of a successful vaccine:

- It should be safe to administer.
- It should induce the right sort of immunity.
- It should be effective against the infectious agent in particular and disease prevention.
- It should have a long shelf life and should be stable.
- It should be affordable by the population at which they are aimed.[5]
- 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 side effects and contraindications.

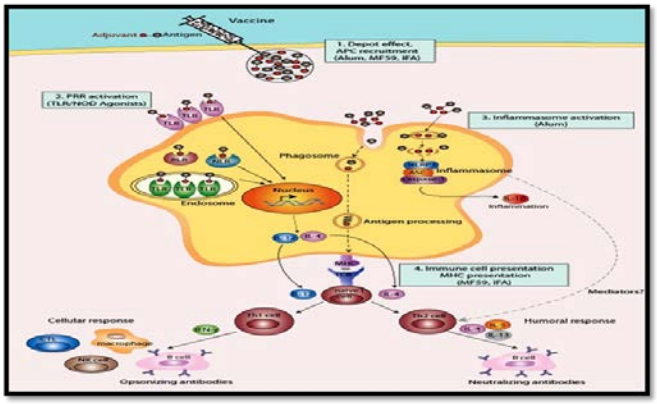
Types of periodontal immunization

Active immunization: Active immunization has carried out using whole bacterial cells, outer components or synthetic peptides as antigens.[7]

- **Whole cells**

Here, the entire cell with its components is inoculated into a host to bring about active immunization.[7]

Mechanism of Action of Vaccine



Active immunization with whole cells might induce exaggerated inflammatory responses in the host. It was found that bone density is significantly decreased in ligated teeth with non-human primates vaccinized with whole-cell antigens of P. gingivalis.[6]

As compared to sham vaccinated animals, mice were immunized subcutaneously with an inactivated, whole-cell vaccine preparation of Porphyromonas denticanis, Porphyromonas gulae and Porphyromonas salivosa displayed significantly reduced alveolar bone loss in response to heterologous and cross-species challenges[8]

Protective mechanism evidence from a formalin-killed whole-cell P. gingivalis vaccine with Syntex adjuvant formulation (SAF) is there in the reported effect that vaccine-induced serum antibody titres to P. gingivalis resulted in a blockage of prostaglandin E2 response to LPS challenge.[9]

Outer components

Subunits which are used for the development of active immunization are the virulence factors of P.Gingivalis include gingipain, fimbriae, capsular polysaccharide and heat shock protein.[10]

Synthetic Peptides

Adhesion mapping, T-cell and B-cell epitopes are essential for investigating synthetic peptide vaccines. T and B cell epitopes are recognized by T cells and B cells, respectively. Adhesion epitope mediates adherence between bacteria and host tissue through a ligand-receptor interaction. It is essential to design a synthetic peptide vaccine in which antigenicity does not imply immunogenicity. Since secretory IgA and IgG may play a role in bacterial adhesion preventing to mucosal receptors or salivary glycoproteins, adhesion epitopes are also indispensable to the immune response elicited by synthetic peptide vaccines.

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

Here, antibodies are produced when antigens are injected into a vector. These antibodies, bring about passive immunization when inoculated into host. Chronic disease is not generally an indication of passive immunization.

Passive immunization can be brought about in two ways:

- Murine monoclonal antibodies
- Plantibodies[6]

Genetic immunization: By the early 1990s, scientists had begun to study new approaches to the production of vaccines that differ in structure from traditional ones. The strategy involves genetic engineering or recombinant DNA technology.[6] DNA vaccines can be administered intra-nasally, intra-muscularly or delivered by gene gun, an instrument that propels tiny DNA-coated gold beads into the body's cells. These recombinant vaccines activate the immune systems eliciting both antibody-type and killer cell type immunity.[4]

There are two types

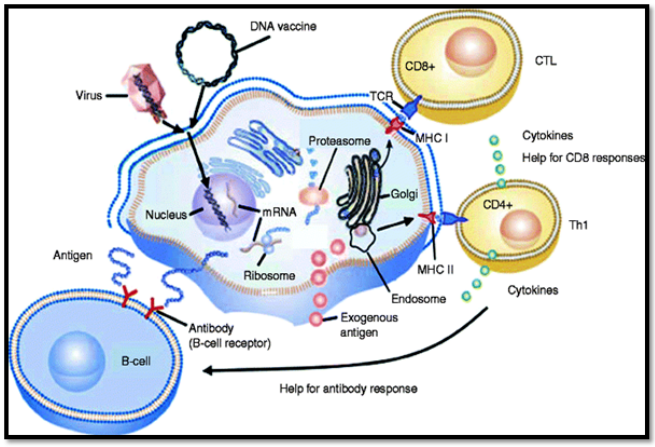
- Plasmid vaccines
- Live, viral vector vaccines.[6]

Other Preventive Strategies Employed For Periodontal Disease

Uses of probiotics: The united nations Food and Agriculture Organization has defined probiotics as "live microorganisms administered in adequate amounts conferring beneficial health effect on host".[11]

It has been seen that despite mechanical sub-gingival debridement in combination with improved oral hygiene, within 1-2weeks of baseline there is a temporary shift toward the less pathogenic composition of bacteria. Within weeks to months there is re-establishment of a more aggressive microbiota. The focus start, therefore on the "absence or reduction of the so-called beneficial bacteria". Decreased number of beneficial bacteria are restoring via probiotics might be of considerable interest in the treatment of plaque related periodontal diseases.

DNA Vaccination



Gene therapy as a future perspective: Insertion of genes into an individual's tissues and cells to treat a disease is gene therapy. In the last decade, research of

gene transfer has led to a novel way to achieve vaccination, as discussed below:

when immunised the salivary gland of the mouse using plasmid DNA encoding the fimbrial gene of P. gingivalis, produces fimbrial protein locally in the salivary gland tissue, resulting in the subsequent production of specific salivary immunoglobulin's, IgA, IgG and serum IgG antibodies and the secreted IgA could neutralize P. gingivalis.

Scientists also demonstrated the efficacy of immunization with genetically engineered S. Gordonii vectors expressing P. gingivalis fimbrial antigen as a vaccine against associated periodontitis in rats of p.gingivalis.

The hemagglutinin gene, which is an important virulence factor of P. gingivalis, has been identified, cloned and expressed in Escherichia coli. The recombinant hemagglutinin B (rHagB), when injected subcutaneously in Fischer rats infected with P. gingivalis, showed serum IgG antibody and IL-2, 10 and 4 productions which gave protection against P. gingivalis induced bone loss.

Vaccine design via fine-tuning of antigen-specific T cells: Helper T-cells polarization depends, in part, on the nature of the antigens, source of adjuvant, duration of the antigenic challenge, presence of co-stimulatory molecules and the type of antigen-presenting cell.[12] The helper T-cells produce enormous amounts of two types of cytokines, Th1 and Th2. Severity of periodontal disease is counterbalanced by the fine-tuning of the array of cytokine profiles contingent and Th1/Th2 on T-cell polarization and immunoglobulin profiles secreted by B lymphocytes.

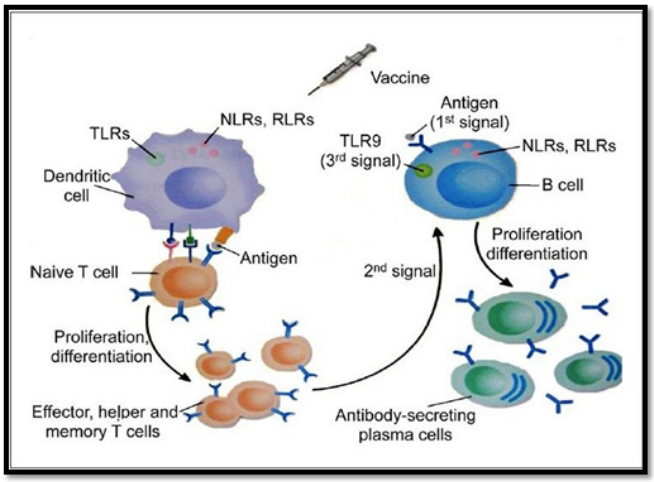
Gemmell and Seymour have shown Th1-dominated lesions in humans are stability associated, while Th2-dominated lesions are progressive disease associated, such that Th2 cells downregulation with a concomitant increase in Th1 responses selectively against the bacteria may have therapeutic effects. However, the polarization of P. gingivalis specific clones or T-cell lines in lesions of periodontal disease is still controversial. Experiments further on immune modulation by pathogen-specific T-cell clones may lead to a greater understanding of the specific role of antigen-specific T lymphocytes in the pathogenesis of periodontal disease at the species level. At this stage it appears that it is the balance between Th1 and Th2 cytokines that take part an important role in maintaining alveolar bone homeostasis.[13]

As an new strategy, vaccines designed to stimulate antigen-specific regulatory T-cells (Tregs, CD4+, CD25+, FoxP3+), secreting IL-10 and tumour necrosis factor-beta (TNF-β), may come up with new clues to prevention of periodontal disease, through the induction of either immune tolerance or effector function.[4]

Vaccine design via immune modulation in the polymicrobial biofilm: Two dissimilar independent research groups have evaluated immune modulation by immunizing F. nucleatum prior to ensuing immunization of P. gingivalis. Immunized mice with F. nucleatum prior to P. gingivalis, a significantly decreased antibody response to P. gingivalis was observed.[14] At the same time, Choi et al. demonstrated that P. gingivalis specific T helper cell clones immunized with P. gingivalis alone which are derived from mice had a Th1 profile while those derived from mice immunized with F. nucleatum before P. gingivalis had a Th2 profile. The second research group also reported that by immunization of F. nucleatum anti-F. nucleatum antibody is elicited prior to P. gingivalis down modulated the opsonophagocytic function of anti-P. gingivalis immune serum.[15]

Vaccine design via commonly shared antigens by selected periodontal pathogenic species

Many of potential antigenic determinants may share sequence homology with other periodontopathic bacteria. These antigens include phosphorylcholine, capsular polysaccharide (CPS), and heat shock protein (HSP). A suitable candidate antigen is, phosphorylcholine. In addition, CPS would require protein conjugation in any vaccine design and is not potent inducer of T-Cell mediated immunity. Therefore HSP antigen, which has identified in most putative periodontal pathogenic bacteria with high level of sequence homology, is a suitable candidate molecule for the development of periodontal vaccine targeting the mixed microbial component.[4]



Vaccine Design via Fine Tuning Of Antigen Specific T-Cells.

Hurdles in periodontal vaccine development:

Though animal models has achieved success, to make the dream of periodontal vaccine a reality for humans, there are several reasons which still have to overcome. Some of them are listed below:

- The periodontal disease has a multifactorial nature. Hence, the elimination of certain bacteria may not prevent the onset and progression of the disease.
- Differentiation between primary colonizers and secondary invaders is accurately difficult.
- The difficulty to grow and identify many of the disease-associated microorganisms and the variability of the plaque composition from one individual to other and between sites in the same individual.
- The normal flora of rodents and presumptive pathogenic microorganisms are members of normal sub-gingival bacterial flora in humans are not indigenous.
- Disease state and chronicity of the disease variations.
- It is clinically detecting and quantitating active periodontal disease difficulty.
- Secretary immune system bathed the gingival sulcus location at the interface between the local immune responsive tissues and systemic immunity, and the oral cavity.
- The nonfatal nature of the disease.[11]

Conclusion

Tried the methods of forms of active and passive immunization. Researches are still carried out to unravel mystery with humans, as none of the modalities are able to incorporated as a complete “vaccine”. The development of the vaccine is dependent on the bacterial antigens identification that are expressed in induction of a protective response and invivo. DNA vaccines that were described <5 years ago have already progressed to Phase I clinical trial in healthy humans. Thus, the current status of our understanding in the field of vaccines against periodontal disease is not complete. Still, extensive research in this direction may hold a promising future in the development of a periodontal vaccine.

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