Review

Periodontal Vaccine: A Therapeutic Modality on the Horizon

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ABSTRACT

Periodontal disease which is poly microbial, is one of the leading causes for tooth loss in the adult population. Current treatment modalities have resulted only in arresting the disease progression but have not cured the disease completely, nor do they prevent the recurrence. Hence there is a need for more sophisticated therapeutic modalities which may include vaccines. Till now, however, no periodontal vaccine trial has been successful in satisfying all the requirements of an ideal periodontal vaccine. Periodontal vaccines not only target a single pathogen, but, since poly microbial, would be a useful adjunct to mechanical therapy.

Key words: host response , periodontal vaccine, periodontitis.

INTRODUCTION

In the current paradigm of periodontal disease, the periodontal pathogens are essential for disease initiation, however, the extent and severity of tissue destruction largely depend on the nature of the host microbial interactions. Periodontal diseases are immune inflammatory responses induced by microorganisms in dental plaque which, harboured within a susceptible periodontium contributes to tissue destruction, bone loss and eventually tooth loss.

Specific molecules have been recognised that signal periodontal tissue destruction as the inflammatory response develops. They can be broadly divided into a) microbial virulence factors b) those derived from host immune inflammatory response. Bacteria are important because they drive and perpetuate the inflammation but the great majority of tissue breakdown results from host inflammatory processes. Microbial virulence factors include

a) lipopolysaccharides
b) bacterial enzymes and noxious products
c) microbial invasion strategies
d) fimbriae
e) bacterial deoxyribonucleic acid and extracellular deoxyribonucleic acid.

The host derived inflammatory mediators can be divided as

a) cytokines
b) prostaglandins and
c) matrix metalloproteinases.

Till date, no preventive modality exists for periodontal disease and treatment rendered is palliative. The availability of periodontal vaccine would not only prevent or modulate the course of periodontal diseases, but also enhance the quality of life of people for whom periodontal treatment cannot be obtained easily.

BACTERIAL ETIOLOGY

Acceptance of the specific plaque hypothesis was spurred by the recognition of A.actinomycetemcomitans as a pathogen in localized aggressive periodontitis.[1] Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans, Treponema denticola, Tanerella forsythus were implicated as the key pathogens in the etiology of periodontal disease.

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According to Loesche WJ in 1976, the specific plaque hypothesis states that only certain plaque is pathogenic, and its pathogenicity depends on the presence or increase in the specific microorganisms.[2]

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.[3]

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.

HOST RESPONSE IN PERIODONTAL DISEASE

The host defense against periodontopathogenic bacteria comprises innate and acquired immunity. Saliva, GCF and the keratinocytes are some of the key agents that play a key role in innate immune response. [4,5]Neutrophils are the primary leukocytes to act in innate immune response. Macrophages and dendritic cells are also important innate immune cells which express pattern recognition receptors (PRRs) that interact with the specific molecular structures on microorganisms called microbe associated molecular patterns (MAMPs) to signal immune responses.[6,7]However innate immune response is nonspecific hence results in excessive host tissue damage without effective antigenic clearance. [8,9]Adaptive immunity has evolved to provide a focused and intense defense against infections that overwhelm innate immune responses in the tissues. [10,11,12] Adaptive immunity is slower and reliant on complex interactions between antigen-presenting cells and T and B lymphocytes, cytotoxic T cells and antibodies.[13,14,15] The increase in antibody titre or antigen specific T –cells resulting from an exposure of a host to an antigen for the first time is referred to as the primary response. The secondary response develops after a subsequent exposure to that same antigen. Because of the generation of memory, the secondary response

- Is more rapid in onset
- Is longer in duration
- Is greater in strength due to higher titres
- For B cells may have greater specificity, against the antigen compared with the primary response.

The expanded pool of memory cells provides a reservoir of cells that is sustained for years by constant stimulation of antigen maintained by follicular DCs (Dentritic Cells). The primary response takes slightly more than one week to become measurable and biologically or clinically useful. Secondary responses are clinically measurable within 1 to 3 days and are so effective that an individual may not be aware of the infection. The immune response to pathogenic microorganisms involves the integration at the molecular, cellular, and organ level of elements often categorized as being part of the innate immune system or the adaptive immunesystem. Periodontopathogens have however developed mechanisms to inhibit and evade cell-mediated and humoral immune responses.[16,17,18]

VACCINE

Vaccine is the name applied generally to a dead or attenuated living infectious material introduced into the body with the object of increasing resistance or eliminating the disease. Vaccination is the development of immunity, or resistance to infection, after a secondary response that is adequate to consider the individual immune to a subsequent infection. The foremost step 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. The antigens of a vaccine induce clonal expansion in specific T or B cells leaving behind a population of memory cells.

Vaccines may be synthetic or natural monovalent or polyvalent .Here the organism is isolated or created and is unable to cause full blown disease. But still retains antigenic components which induce host immune response. Vaccines may be prepared by

a) killing the organism using formalin-called inactivated or killed vaccine.

b) by using only antigenic part of the disease causing organism, for example the capsule, the flagella ,the part of the protein cell wall-acellular vaccines.[19]

c) vaccines may be prepared by weakening a live microorganism by aging it or altering growth conditions-attenuated vaccines.[19]

d) toxoids are vaccines from toxins ,which are adsorbed onto aluminium salts to decrease their harmful effects and is administered with an "adjuvant" which can have effects on antigen delivery ,immune modulatory cytokines ,and antigen –presenting cells.[20]

Characteristics of an effective vaccine include safety, protectivity, the ability to provide sustained protection, stimulation of protective T-cells and the ability to produce neutralizing antibodies. Practical considerations like cost-effectiveness, biological stability, access and minimum contraindications and side effects are also important.[21]

PERIODONTAL VACCINE

In the early twentieth century, three periodontal vaccines were employed which include pure cultures of streptococcus and other organisms, autogenous vaccines, stock vaccines. Examples include Vancott's vaccine and Inava endocarp vaccine.[22]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. . Most experiments on immunization of periodontitis, despite its poly–infectious nature, have been directed towards a very limited number of antigenic components of a single specific pathogen; either P.gingivalis or A.actinomycetemcomitans. P.gingivalis is the most potential vaccine candidate because this pathogen carries several high-potent antigens, a lipopolysaccharide (LPS) capsule, lipids, and outer membrane proteins (OMP) which are used as subunits for development of active immunization.[23]

Types of periodontal vaccination

Active immunization.[24]Here, an individual immune system is stimulated by administrating killed or live attenuated products derived from micro-organisms (table 1). 1 It is further classified as

- Whole bacterial cells eg: P. Gingivalis whole cells. Elevation of serum antibodies to whole cells and partially purified fimbriae from P.gingivalis were elevated in rats immunized with P.gingivalis cells. Further activities of collagenase and cystein proteinases in periodontal tissues losses was decreased.[25]It has also been reported that formalin killed whole cells of P.gingivalis vaccine has resulted in blockage of PGE_2 response to LPS challenge.[26]
- Sub unit vaccines e.g. using virulence factors of P.gingivalis such as gingipains. P.gingivalis produces two classes of cysteine proteases that have been implicated in periodontal pathogenesis. These are known as gingipains and include lysine specific gingipain Kgp and the arginine specific gingipains RgpA and RgpB. The gingipains can modulate the immune system and disrupt immune inflammatory responses potentially leading to increased tissue breakdown.[27]It has been reported that immunization with gingipains prevents colonization with P.gingivalis and reduces bone loss.[28]
- Synthetic peptides eg: fimbrial peptide in the gnotobiotic rat model. Synthetic peptides based on the protein structure of fimbrillin inhibit the adhesion of P.gingivalis to saliva coated-hydrxyapatite crystals in vitro and their binding domains are located at the carboxyl terminal region.[29] (fig.1)

Passive immunization: This approach employs preformed antibodies administered to "at risk" individuals or to individuals during "at risk" intervals to interfere with microbial pathogenic processes. Here antigens are injected into a vector that produces antibodies. (Table 2) These antibodies were inoculated into host to bring about passive immunization. Passive immunization has shown to temporarily 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. (fig.1)

Genetic immunization: Here, DNA plasmids encoding genes required for antigen production are transferred to an individual. It can be divided as:

- Plasmid vaccines: plasmids are fused with the DNA of a particular pathogen and inoculated in animal for antibody production, however it may cause oncogenesis.

- 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. Those vectors enter the body cells, produce proteins and induce humoral or cellular immune response. (fig.1)

Table 1: Summary of findings from animal study models for active immunization vaccine trials in periodontitis .[30]

BACTERIA	VIRULENCE FACTOR	AUTHOR
P. gingivalis	Whole-cell	Persson et al. (1994)
	Fimbriae	Evans et al. (1992)
	Gingipains(RgpA & Rgp B)	Moritz et al .(1998)
	Gingipain R	Genco et al. (1998)
	Gene vaccine	Ross et al. (2004)
	Whole-cell +Rgp	Gibson III et al. (2001),Rajapakse et al. (2002)
	E.coli cloned with P.gingivalis sequence	DeCarlo et al. (2003)
A.actinomycetemcomitans	Leucotoxin	Ebersole et al. (1990)
F. nucleatum & P. gingivalis in combination		Gemmell et al. (2004)

Table 2: Summary of findings from human studies on passive immunization in subjects with aggressive periodontitis or chronic periodontitis.[30]

BACTERIAL ANTIGEN	AUTHOR AND STUDY TYPE
P. gingivalis A. viscosus P. intermedia T. vincentii T. denticola	Aukhil et al. (1988)
P. gingivalis A. viscosus A. actinomycetemcomitans (serotype a) P. intermedia	Kohyama (1989)
P. gingivalis	Chen et al. (1995)
P. gingivalis	Johnson et al(1993)
A. actinomycetemcomitans	Sjo¨stro¨m et al. (1994)
P. gingivalis	Mooney et al. (1995)

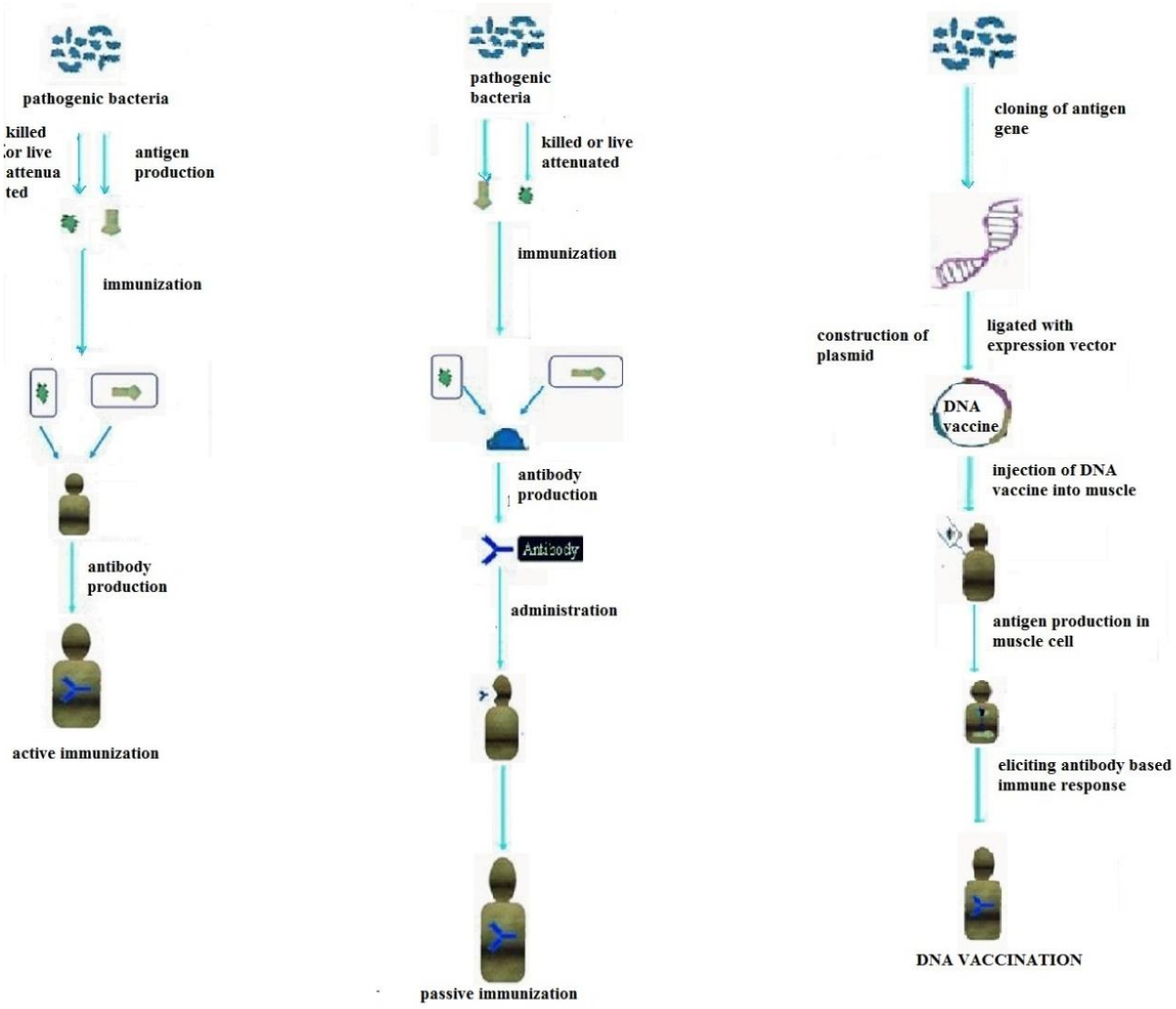

Fig 1: Pictorial representation of active immunization, passive immunization and DNA vaccination

CHALLENGES IN PERIODONTAL VACCINE DEVELOPMENT

1. Multiplicity of pathogenic microorganism indicates that vaccine design against periodontitis could be very complex.
2. Bacterial whole cells or crude extracts preparation for vaccination is not desirable because the antigenic determinants of bacteria potentially posses a high risk of cross-reactivity with human counterparts.
3. Vaccines may be contaminated with unwanted proteins or toxins, or even live viruses causing a threat especially to hypersensitive individuals.
4. Supposedly killed vaccines may not have been properly killed; attenuated vaccines may revert to the wild type.[31]This could be of serious concern in an immunocompromised recipient.
5. Animal models for vaccine trials may pose inconsistencies with human models in major histocompatibility complex –restriction of antigens presented by antigen presenting, thus obscuring immunomodulant epitopes.

FUTURE ADVANCES

1. A genetically engineered obese diabetic mouse is a valuable tool for the study of periodontal disease and putative periodontal vaccines.[32]
2. Vaccines using cross reactive immunodominant epitopes as antigenic molecules in an attempt to stimulate antigen–specific regulatory T –cells, secreting IL-10 and Transforming growth factor β, may provide new clues for periodontal disease prevention, through the induction of either immune tolerance or in effector function.[33]
3. Strategies to enhance immunogenicity of antigenic components of B or T lymphocytes such as immunization of dentritic cells pulsed with antigens, use of improved adjuvant formulas, use of plantibodies and the use of transgenic microorganisms as antigen vectors.

CONCLUSION

However, the elimination of the periodontopathogens does not eliminate the periodontal disease as proposed in the ecological plaque hypothesis. It states that any change to the environment induces a response in the micro flora, and vice versa. Implicit in this hypothesis is that, although disease can be treated by targeting the putative pathogens directly.[34] However, long-term prevention will only be achieved by interfering with the underlying changes in the environment that drive the deleterious shifts in the micro flora. However vaccines targeting the polymicrobial etiology of periodontal disease could act as an important adjunct to mechanical debridement. Hence the concept of periodontal vaccination is not a myth but a reality which will come true in the near future if research is carried out in the right manner in the right direction.

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