Rama Univ. J. Dent. Sci. 2022 December; 9(4):-21-28 ISSN No. 2394-417X (print), 2394-4188(online)

Periodontal Vaccine

Hiroj Bagde[1], Nikhat Fatima[2], Lynn Johnson[3], Rupma Singh[4]
[1-3]*Reader, Dept of Periodontology; Rama Dental College, Kanpur,.*
[4] *student, Dept of Periodontology; Rama Dental College, Kanpur,.*

Abstract

Recent progress in cellular and molecular biology has led to the development of new approaches for vaccinations against a wide variety of infectious diseases. These approaches have the potential to prevent infection in humans. It has been known for a very long time that people who successfully recovered from a sickness went on to build subsequent resistance to that disease. Edward Jenner is credited for developing and establishing the notion of vaccination in the late 18th century. He did so by making use of the cross protection offered by the cowpox virus, which does not cause disease in humans. We have the potential to analyse all of the genes and proteins from any human disease because to the rapid rise of microbial genome sequencing and bioinformatics analysis tools. This is possible because of the quick expansion of these fields. This method has the potential to present us with fresh targets for the development of antimicrobial medications and vaccines. However, in order to actualize this potential and pick these targets from the plethora of available candidates using modern bioinformatics and experimental methods, which are necessary steps, the method of inducing specific immune resistance to fight off an infection caused by bacteria or viruses is called vaccination. This review article encompasses the literature review of periodontal vaccine.

Introduction

An accidental observation that chicken cholera bacillus cultures left on the bench for several weeks lost their pathogenic property but retained their ability to protect the birds against subsequent infection by them led to the discovery of the process of attenuation. Louis Pasteur attenuated cultures of anthrax bacillus by incubation at high temperature (42-43 c) and proved that inoculation of such cultures in animals induced specific protection against anthrax.[1]

The success of such immunization was dramatically demonstrated by a public experiment on a farm at Pouilly-le-fort (1881) during which vaccinated sheep, goats and cows were challenged with a virulent anthrax bacillus culture. All the vaccinated animals survived the challenge, while equal number of unvaccinated control animals succumbed to it. It was Pasteur who coined the term VACCINE for such prophylactic preparations to commemorate the first of such preparations, namely cowpox, employed by Edward Jenner for protection against smallpox.[2]

As the successful vaccination against smallpox started in 1796, the importance of prophylactic immunization against infectious diseases is well understood. Effective vaccines have successfully eradicated or significantly reduced the prevalence of several diseases, especially in developed countries. These include the (I) Bacillus–Calmette–Guér in vaccine against tuberculosis and cholera using live attenuated or killed bacteria, (II) polio and rabies vaccines using live attenuated viruses, (III) tetanus and diphtheria vaccines using bacterial cell antigen subunits, (IV) Haemophilus influenza, and pneumococcus infections using conjugated vaccines, and (V) synthetic vaccines, i.e. (HBV) against Hepatitis B.

Vaccines [3]

A vaccine is a live attenuated or killed microorganisms or parts or products from them which contain antigens that can stimulate a specific immune response consisting of protective antibodies and T cell immunity.

A vaccine should stimulate a sufficient number of memory T and B cells to yield effector T-cells and antibody-producing B cells from memory cells. Viral vaccine should also be able to stimulate high titres of neutralizing antibodies. Vaccines can prepared from weakened or killed microorganisms; subcellular segments; inactivated toxins; toxoids derived from microorganisms or immunologically active surface markers extracted from microorganisms.

They can classified be as viral vaccines and bacterial vaccines according to the pathogens to which they are directed.

Bacterial vaccines-

- Typhoid-paratyphoid
- Cholera
- Whooping cough
- Heamophilus influenza
- Bacillus Calmette Guerin etc.

Viral Vaccines-

- Poliomyelitis inactivated
- Rabies
- Influenza
- Hepatitis
- MMR

They can be administered intramuscularly, subcutaneously, intradermally, orally or intranasally as single agents or in combination.

An ideal vaccine should be effective, well tolerated easy and inexpensive to produce, easy to administer and convenient to store.

Approaches to vaccine design.

Intact pathogen

Heat killed or chemically denatured

Attenuated by growth conditions or genetic manipulations

Subunit vaccines

- Recombinant proteins
- Synthetic peptides

Vaccine vehicles

Live vectors: viral (eg.adenovirus) and bacteria (eg. Mycobacteria)

Adjuvants

- Conjugated to lipid or protein carrier molecules
- Microencapsulated in lipids

DNA immunization

Injection of plasmid DNA

Maybe the most important discovery in recent vaccine development is new knowledge on the gene coding for bacterial protein antigens (attenuated vectors) that can be inserted into cells of other bacteria. Once inserted, these bacteria produce large volumes of the antigen protein used in new vaccines (i.e. hepatitis B surface antigen, lyme disease, pertussis and cholera vaccines). Serial inoculations of vector-based proteins or plasmid DNA vaccines have the potential to induce both strong B- and T-cell responses. Especially in virus research, the development of attenuated vectors and the use of orally administered fruits or vegetables containing vaccine antigens as the route of administration is in progress (Plotkin & Plotkin 1999, Hilleman 2000).

Vaccination

Is the induction of the active (Protective) immunity in man or other animals against infectious disease by the administration of vaccines (inoculation).

Guidelines for immunization against infectious disease.

- The principal contraindication to inactivated vaccines is a significant reaction to a previous dose.
- Live vaccine should not be given to pregnant women or to the immunosuppressed, or in the presence of acute infection.
- If two live vaccines are required, they should be given either simultaneously in opposite arms or 3 weeks apart.
- Live vaccines should not be given for 3 months after an injection of human normal immunoglobins (HNI).

Immunological adjuvants (i.e. lipopeptides, lipopolysaccharides (LPSs), heat-shock proteins (HSP), or zymosan – a mixture of yeast cell wall polysaccharide, proteins, and ash) as substances used in combination with specific antigens in vaccines are used to amplify T-cell immune responses or to absorb complement C3. Freund's adjuvant and other composite adjuvants are also commonly used in vaccines. Syntex adjuvant formulation (SAF) has been used as an alternative to Freund's complete adjuvant. SAF is an oil-in-water emulsion stabilized by Tween 80, and pluronic polyoxyethlene / polyoxypropylene blocks copolymer L121. SAF activates complement by the alternate pathway and is more effective with hydrophobic proteins (Chiron Corporation, Emeryville, CA, USA). Animal studies have demonstrated that adjuvants often interact with Toll-like receptors and activate macrophages, monocytes, and leucocytes, resulting in stimulated secretion of inflammatory products (i.e. TNF-α, IL-8, hydrogen peroxide and arachidonic acid. Thus, adjuvants can have effects on antigen delivery, induction of immune modulatory cytokines, and effects on antigen-presenting cell. The choice of adjuvant may partly explain differences in vaccine trial outcomes.

Serious concerns regarding the production, purity, content, and safety of vaccines since the early 1900 standards for assessing the safety and efficacy have challenged the development of new vaccines. No vaccine is perfectly safe. The US Food and Drug Administration (FDA) have provided basic regulatory criteria for vaccines. The "benefit to risk" consideration must specifically be considered in the review of new vaccines. New vaccines are partly monitored by vaccine-adverse event surveillance methods using computer data mining.

Because of the fact that vaccine development is expensive and time consuming, coordinated support from funding agencies, such as the US National

Institutes of Health, and commercial interests are necessary to develop and assess the efficacy, safety, and utility of new vaccines. Between 1990 and 2002, the funding support for vaccine research increased from approximately 200 million US$ to 1.4 billion US$. In the year 2002, the Center for Biologics Evaluation and Research and FDA listed 42 vaccine studies in phase III trials, with more than 300 ongoing vaccine basic research and development projects. Some of these vaccine projects include work using purified proteins, LPS, surface lipoproteins, carbohydrates, and lipid A. Knowledge acquired through such efforts may be indirectly applicable for periodontal vaccine studies. In the development of a new vaccine, it would be important to consider the target population in which the vaccine may have an impact, regulatory factors, outsourcing (basic research, early pre-clinical and clinical work, manufacture, sale), competition, and funding of vaccine projects. These barriers may explain why periodontal vaccine research has been slow to progress.

The FDA requires extensive research and testing before a vaccine can be licenced for general use. Once target antigens have been identified, purified, and prepared for the vaccine, pre-clinical testing in animal models (mice, rats, rabbits, guinea-pigs, or monkeys) is required. Primary safety testing is often specifically studied in guinea-pigs. Before any vaccine can be tested in humans, an investigational new drug application must be approved by the FDA. Specifically, information on how the vaccine works, how it is manufactured, and safety and efficacy data from the animal studied must be provided. Following such approval, phase I safety studies are often performed in less than 20 healthy subjects. Then, phase II efficacy studies with 50–200 subjects are performed, and if successful, are followed by phase III studies of up to several thousand subjects to test the vaccine power in preventing the disease. It might take up to 50 years before a vaccine project can obtain a Biologics Application (BLA) approval. Currently, periodontal vaccine trials that go beyond testing principles in animal models have not been performed.

Vaccines and host response [4]

The host responses to infectious exposures and from non-infectious substances are physiological functions of the immune system. Specifically, microbial substances including lipids, proteins and polysaccharides trigger immune responses that either eliminate the pathogens or non-self substances, or result in pathological consequences for the host. Prior to the very first infection, from birth, existing innate immunity functions protect the host and provide competent responses to microbes. The innate immune system includes the following: (I) epithelial cell and chemical barriers (defensins), (II) phagocytic and natural killer cells, and (III) serum proteins, complement factors, and cytokines. Virulent microorganisms equipped with sophisticated self-protective and destructive abilities can bypass the innate immune system.

As a second line of host defence, adaptive immunity has explicit capacities to recognize, memorize, and with increasing efficacy, respond to exposures of microorganisms and their by-products (antigens and enzymes). Adaptive immunity consists of two immune competent systems developed by lymphocytes: (I) the cell-mediated immune system, and (II) the humoral immune system. The cell-mediated immune system is mediated by T lymphocytes, and is specifically dedicated to interact with viruses and bacteria that survive and proliferate inside cells (i.e. phagocytes and epithelial cells). Antibodies that explicitly interact with specific external bacteria and their antigens are produced by B lymphocytes. Such antibodies target circulating and non-invading microorganisms and their toxins via binding through various mechanisms. Thereby, the immune system can neutralize and/or eliminate most pathogens. Interactions between these immune systems occur. The B-cell immune interaction has specific interest for periodontal immunization. Current evidence suggests that most pathogens associated with periodontitis are located in the periodontal pockets and are external to host cells. One of the key questions asked is whether a host humoral antibody immune response is protective, destructive, or irrelevant to periodontal infections. Under the assumption that humoral immunity is protective, the perspective of a vaccine to protect against periodontitis would be obvious.

Periodontitis

The early colonizing bacteria on teeth and on gingival tissues include predominantly Neisseria, Streptococci, and Actinomyces species. Immunization against such bacteria with the objective of preventing colonization of later colonizing pathogens is currently unrealistic. The later phases of bacterial colonization occur in complex biofilm structures. Thus, different from diseases caused by specific single-type infections and against which vaccines have been successfully developed, the aetiology of periodontitis is a complex mixed infection that includes large numbers of different pathogenic organisms. The bacteria most frequently associated with periodontitis include

Porphyromonas gingivalis, Prevotella intermedia, Tanerella forsythia (forsythensis), Treponema denticola, Actinobacillus actinomycetemcomitans, and Fusobacterium spp. Such bacteria and their by-products can elicit strong immune responses.

Bacteria in biofilm structures can be protected from host immune responses and are dependent on environmental (passive response) and genetics (active response) factors. Changes and disconnection from biofilms occur via (I) swarming dispersal in which individual bacteria are released, (II) clumping dispersal in which aggregates of bacteria are released, or (III) surface disposal in which bacterial biofilms move across surfaces. All three models will challenge the host immune system in different ways. For example, A. actinomycetemcomitans has a non-motile pathogen that appears to be released passively from biofilm structures by the swarming disposal model and is thereby protected against most host immunity functions...

P. gingivalis has been considered as a key pathogen in periodontitis. In vitro studies have demonstrated that P. gingivalis has the ability to invade gingival epithelial cells thereby obtaining protection against humoral immunity factors. P. gingivalis interacts with several aspects of the immune system. In fact, P. gingivalis can modulate its surface fimbriae dependent on access to them and whether the pathogen resides in an extra- or intracellular position. This might be one of the mechanisms by which P. gingivalis is evasive to host immunity.

Successful implantation of a rifampin-resistant strain of P. (Bacteroides) gingivalis into periodontal pockets of monkeys (M. fascicularis) caused an increase in the systemic levels of antibody towards the microorganism. It also resulted in alveolar bone loss. This observation raised questions on whether antibodies against P. gingivalis were destructive or protective. Apparently, the natural host immune response failed to provide protection against the infection. If the principles from other vaccines also apply to periodontal infections, active immunization against P. gingivalis infection might be feasible and may raise protective immunity against periodontitis.

Vaccine candidate antigens of P. gingivalis [5]

P. gingivalis is a potential vaccine candidate because this pathogen carries several high-potent antigens, an LPS capsel, lipids, and outer membrane proteins. Whole-cell formalin-killed P. gingivalis has been used as the target antigen. In one study, attempts were made to combine antigens from several bacteria. The results were not conclusive. Shared antigenic determinants (epitopes) exist for many Gram-negative anaerobes. Especially, cell wall surfaces that display polyvalent arrays of protein or carbohydrate antigen determinants in a spatial arrangement may influence antibody binding with cross-over effects. The fact that different bacteria share antigenic determinants would make it feasible to use antigens from a key target pathogen present in the oral biofilm. A major virulence factor of P. gingivalis is the extracellular non-covalently associated complexes of Arg-X- and Lys-X-specific cysteine proteinases and adhesins designated the RgpA–Kgp complexes. Studies have shown that immunization with RgpA–Pgp induces an immunoglobulin G2a response and with a restricted colonization by P. gingivalis and periodontal bone loss in the rat.

Through sequencing DNA processes, bacterial genome bioinformatics on P. gingivalis outer membrane proteins have made it possible to study potential periodontitis vaccine benefits in murine models. This includes the outer membrane protein, porin (PG33) and (PG3), as well as cysteine proteases (PG32) and (PG57) (Ross et al. 2001). Studies with these proteins have shown promise and have shown protection against P. gingivalis infection (Ross et al. 2004a, b). Studies have also demonstrated that transcutaneous immunization of mice with a 40 kDa outer membrane protein of P. gingivalis induces specific antibodies that inhibit coaggregation by P. gingivalis to Streptococcus gordonii.

Large variations in P. gingivalis ribotypes recognized by serum immunoglobulin G (IgG) from subjects with chronic periodontitis also exist. Some outer membrane proteins may be shared by ribotypes (i.e. the 44 and 27 kDa proteins) (Sims et al. 1999). Studies of clinical isolates of T. forsythia have also demonstrated a large and subject-defined genotypic variation for T. forsythia (Persson et al. 2000). P. gingivalis FDC 381 possesses a 53 kDa protein antigen (Ag53) on its outer membrane, which evokes a strong humoral immune response in many patients with periodontal disease, but the humoral immune responses to Ag53 differ greatly among patients and are a result of major B-cell epitopes.

Animal models

Vaccine trials in animal models are required for safety and efficacy testing of vaccines. The ideal animal research model for vaccine trials against periodontitis with naturally occurring periodontitis based on the same aetiology, pathogenesis, and prevalence in animals as well as in humans does not exist. As substitutes, experimentally induced

periodontitis models have been explored. Some of these may not necessarily provide access to clinical conditions that can readily be assessed for clinical efficacy. Page & Schroeder (1982) concluded that because of continuous eruption patterns of teeth and alveolar bone changes, mice, rats, and hamsters might not be suitable for clinical periodontitis vaccine efficacy studies.

Dogs have not been considered for periodontal vaccine studies. It is of interest that sheep (ovine) appear to develop naturally occurring periodontitis. At least for P. gingivalis in sheep, there is homology to human strains. There is also a similarity in humoral immune responses and periodontitis responses in sheep and humans.

Non-human primates, including M. fascicularis, M. nemestrina, Marmosets, Baboons, and Chimpanzees, have been considered for periodontal vaccine trials. Naturally occurring periodontitis in M. fascicularis (wild caught or domestically bred) is less than 5%. Studies have demonstrated that key pathogens associated with periodontitis can be identified in samples taken from adult M. fascicularis and M. nemestrina and identified by DNA probes aimed for studies of strains found in humans. Thus, the patterns of bacterial presence in older versus young M. nemestrina are consistent with what is known from bacterial patterns in humans. Higher serum IgG titres against key pathogens associated with periodontitis, suggesting an impact over time from exposure, can also be found in older M. nemestrina. In order to predictably induce periodontitis in non-human primates, the experimentally induced periodontitis model has been used.

Active immunization

Active immunity is induced by exposure to a foreign antigen. This activates lymphocytes to produce antibodies against the antigen. The immune system of the host plays an active role in responding to the antigen.

Vaccine studies in animal models against periodontitis [6]

Non-human primate vaccine studies

In the guinea-pig model, the safety of a vaccine against periodontitis composed of formalin-killed whole-cell P. gingivalis and the SAF (Syntex, Palo Alto, CA, USA) has been tested. Unpublished data from the vaccine trials at the University of Washington (R. C. Page, R. P. Darveau, G. R. Persson, personal communication) necropsy revealed no organ abnormalities or residual organ effects (kidney, liver, eye balls, lymph nodes). However, Western blot analysis demonstrated that specifically protein and carbohydrate antigen residues were recognized in immunized animals.

The ligature-induced model using M. fascicularis for studies of experimental periodontitis has the advantage that it allows for clinical assessments of oral and periodontal conditions consistent with human examinations. The model also allows for the use of standardized intra-oral dental radiographs.

Vaccine strategies that only prevent colonization of one pathogen may have limited value if they are only effective against one bacterial species. Shared epitopes in lipid A and core carbohydrate of LPS between these two pathogens exist, which makes it feasible to induce immunity to more than one pathogen, although only antigen from a specific bacterial species is used as target antigen in the vaccine.

Results from active immunization studies using an experimental periodontitis model in M. fascicularis demonstrated that the relationship between antibody titres and killing abilities, and protection against challenge with P. gingivalis infection in the non-human primate model is complex.

A wide variability in functional capacity of sera from individual M. fascicularis has been reported. Unique differences, however, in immunogenic potential by different pathogens associated with periodontitis have also been demonstrated in non-human primates. This suggests that the ability of the immune system is highly dependent on the characteristics of antigens produced by oral bacteria.In a blinded, randomized-controlled case–control study over 44 weeks, immunization of M. fascicularis with formalin-killed whole-cell P. gingivalis (strain 5083) vaccine with SAF adjuvant or placebo adjuvant only resulted in significant differences in alveolar bone loss. This was assessed by both computer-assisted density image analysis and by standard bone height measurements, suggesting protection in experimentally induced periodontitis.

The studies demonstrated that, in control monkeys, no significant IgG, IgA, or IgM titres were elevated. In contrast, serum IgG and IgA titres to P. gingivalis appeared early and persisted throughout the 36-week observation period. In immunized M. fascicularis, IgM titres were elevated until 6–12 weeks and then decreased through week 36. Significant opsonic capacity was seen by 6–12 weeks and persisted throughout the study in immunized animals, whereas sera from control animals showed only low opsonization capacity. Moreover, no correlation was seen between peak IgG titres against P. gingivalis and protection against bone loss,

whereas a significant association was found between protection against bone loss and pre-immunization IgM titres to P. gingivalis.

Stimulation of humoral immunity by treatment

Stimulation of self-antibody production as a consequence of treatment of infected tissues causing bacterimea can induce an elevation of antibodies against a target antigen. Studies of serum IgG antibodies to whole-cell protein, and purified LPS fractions of A. actinomycetemcomitans from patients diagnosed with aggressive periodontitis (AgP), but untreated, and from healthy controls have demonstrated large variation in titres (Ou et al. 1997). In a case–control study of subjects with AgP, Chen et al. (1995) demonstrated that non-surgical treatment-induced antibody avidity and elevation of serum antibody titres to both purified LPS and to protein fractions from whole-cell P. gingivalis. This is consistent with a concept that patients with AgP and with initially low functions and levels of antibodies to A. actinomycetemcomitans can be stimulated to produce biologically functional antibodies during the course of non-surgical periodontal therapy. Studies on the one-stage non-surgical debridement suggesting a Schwartzman reaction after treatment also suggest that such a treatment causes bacteraemia, which turns on a host immune response (Quirynen et al. 1999).

Contradictory results have been reported, in that some studies suggest that enhanced immunity occurs as an effect of therapy (Sjöström et al. 1994, Chen et al. 1995, Mooney et al. 1995). Other studies have failed to demonstrate such an effect (Aukhil et al. 1988, Johnson et al. 1993, Horibe et al. 1995, Smith et al. 1996, Darby et al. 2001). Mooney et al. (1995) demonstrated that periodontal therapy affects the magnitude and quality of the humoral immune response. Mooney et al. (1995) also demonstrated that the immune response to treatment is linked to pre-treatment antibody titre levels and that sero-positive subjects responded clinically better to treatment than sero-negative subjects. No significant post-therapy effects on the humoral immune response other than reduced antibody avidity to P. gingivalis and P. intermedia have also been demonstrated (Darby et al. 2001). The observations by Papapanou et al. (2001, 2004) also suggested a correlation between serum titre status and the antibody responses to periodontal microbiota but in relation to the severity of periodontitis.

Apatzidou & Kinane (2004) failed to demonstrate that non-surgical periodontal therapy performed as either full-mouth or sequential debridement resulted in increased antibody titres or avidities to pathogens associated with periodontitis. A trend towards reduction in titres was noticed, and with a marked inter-subject variability. Similar results have been demonstrated for antibody titres to HSP (human HSP60 and P. gingivalis GroEL, a bacterial homologue of human HSP60) (Yamazaki et al. 2004b).

Thus, whether therapy can trigger effective immune responses enhancing resistance to disease and elimination of pathogens remains unclear.

Differences in antigen/antibody complexes studied, differences in serum assays used, differences in periodontitis disease severity classification and existing subgingival microflora, and differences in therapy efficacy are some of the factors explaining the disparate results.

Passive immunization

Protective immunity can be obtained through passive immunization. This can be obtained by transfer of specific antibodies against the target bacteria (antigen). A passive immune response can be achieved by transfer of antibodies via serum, lymphocytes from immunized individuals, or monoclonal antibodies against specific pathogens. Transfer of maternal antibodies to the foetus is another example of passive immunization. The advantages of using antibody molecules to treat infectious diseases include their specificity and versatility (i.e. neutralizing toxins and viruses, activating complement, and opsonization) have been demonstrated (Casadevall et al. 2004). Passive immunization is short-lived and remains effective only as long as the injected antibody persists. The host will not respond to the immunization.

Animal studies

The murine monoclonal antibody Guy's 13 recognizing S. mutans and S. sobrinus has successfully been used to prevent colonization of S. mutans in non-human primates (Lehner et al. 1985). Based on the murine monoclonal antibody Guy's 13, it has been possible to develop a human derivate that has demonstrated binding to the surface adhesion of S. mutans in vitro. It has therefore been suggested that this vaccine candidate may be a useful passive immunization candidate against caries (Kuepper et al. 2005). In vitro testing of a recombinant (r)40 kDa outer membrane protein derived from immunizing mice with purified r40 kDa OMP has demonstrated that the IgG1 monoclonal antibody (Pg-ompA2) is bactericidal against P. gingivalis strain W381 (Katoh et al. 2000). Thus, Pg-ompA2 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 (Teshirogi et al. 2003). Other monoclonal antibodies have been used by oral or intra-nasal immunization of mice with P. gingivalis-coated monoclonal antibodies, demonstrating differences in antigenic specificity of anti- P. gingivalis serum IgG (Van Tilburg et al. 2001). Similar results in mice have also been obtained from passive immunization with monoclonal antibodies against the A. actinomycetemcomitans Y4 strain (Herminajeng et al. 2001).

Promising results have been reported using monoclonal antibodies (MAb 61BG 1, 3) that are specifically recognized by at least 22 laboratory strains and 105 clinical isolates of P. gingivalis. Passive immunization with MBb 61BG 1, 3 resulted in the suppression of P. gingivalis for at least 6 months (Booth et al. 1996, Kelly et al. 1997). Recent construction of a human monoclonal antibody (HuMAb-HMGD1) that is capable of recognizing the 43 and 49 kDa proteins from P. gingivalis and inhibiting the haemagglutinating ability of P. gingivalis may prove useful in passive immunization against periodontitis (pending safety and efficacy studies) (Kaizuka et al. 2003). If selective inhibition of pathogens associated with periodontitis can be induced by topical application of a preparation containing monoclonal antibodies or attenuated vectors in combination with proteins or DNA vaccines it may elicit strong B- and T-cell responses. Such efforts are currently being pursued in other fields (tuberculosis research) and may also become applicable in periodontal research and clinical prevention.

Probiotics [7]

Probiotics are live microorganisms administered in adequate amounts with beneficial health effects on the host. The Food and Agriculture Organization of the United Nations has defined Probiotics as "live microorganisms administered in adequate amounts conferring beneficial health effect on the host".

Most probiotic products contain bacteria from the genera *Lactobacillus* or *Bifidobacterium*, although other genera, including *Escherichia*, *Enterococcus*, *Bacillus*, and *Saccharomyces* (a yeast), have been suggested as probiotics. Such bacteria are often identified from the human gastrointestinal system. These bacteria are purified, grown to large numbers, concentrated to high doses, and preserved. They are provided in products as (1) a culture concentrate added to a food (usually a dairy product) with a low or no opportunity for culture growth, (2) inoculants into a milk-based food (or dietary supplement) as fermented food, or (3) dietary supplements such as powders, capsules, or tablets. There are currently no published reports in the English language on the use of probiotics in the treatment of periodontitis. Mucosal immune responses may be invoked by probiotic immunization. Studies of adhesion molecules have shown that superficial cell layers of the gingiva can be affected and can be stimulated to enhance the presence of immune potent cells (Lappin et al. 2003). Regulation of microflora composition (e.g. by probiotics and prebiotics) may offer the possibility to influence the development of mucosal and systemic immunity, but it can also play a role in the prevention and treatment of diseases such as periodontitis and heart disease (Tlaskalova-Hogenova et al. 2004).

Non-conclusive short-term beneficial effects of a probiotics in the form of cheese containing *Lactobacillus rhamnosus* GG, ATCC 53103 (LGG) in reducing *S. mutans* and yeast counts have been demonstrated in humans (Ahola et al. 2002). However, others have shown increases of lactobacilli and no impact on S. *mutans* in subjects who received administration of probiotics, both in capsule and in liquid form. The increased salivary counts of *lactobacilli* may indicate the need to closely monitor the dental health of patients undergoing long-term probiotics treatment (Montalto et al. 2004).

A link between periodontitis and systemic disease with impending shared vaccine benefits [4,7]

A potential association between stress and periodontitis in humans has been suggested (Pistorius et al. 2002, Merchant et al. 2003). It is therefore of interest to notice that lower serum IgG1/IgG2 ratios against P. gingivalis were found both in immunized and sham-immunized mice as compared with non-stressed animals (Houri-Haddad et al. 2003). This observation may also have implications for the interpretation of data from vaccine studies in animals in general.

There is evidence that microbial HSP are immunodominant antigens of many microorganisms. HSP (i.e. HSP60, GROEL) have been associated with atherosclerosis and Chlamydia pneumoniae infection (i.e. Chiu et al. 1997). Elevated antibody levels against C. pneumoniae, human HSP60, and mycobacterium HSP65 have been identified in subjects with myocardial infarction and ischaemic heart disease (Heltai et al. 2004). The 60 kDa HSP has been associated with delayed-type hypersensitivity responses, and the isolation and sequence analysis of HSP60 from bacteria are important (Kikuta et al. 1991).

Elevated serum antibody titres against human HSP60 and P. gingivalis HSP60 in subjects with cardiovascular disease and periodontitis and with T-cell clonality between these HSP60 proteins have been shown (Yamazaki et al. 2004a). In a pilot project, Yamazaki et al. (2004b) also demonstrated significant variation in antibody titres to HSP60 after periodontal treatment. Other studies have shown that subjects with high anti-HSP (HSP90, DnaK, and GroEL) antibody concentrations tended to have significantly healthier periodontal tissues (Lopatin et al. 1999). Thus, it might be feasible to develop a vaccine against periodontitis based on P. gingivalis-specific HSP or HSP epitopes.

Other studies have demonstrated that Campylobacter rectus and Heliobacter pylori share common antigens belonging to the HSP60 family of antigens. H. pylori has been linked to several chronic diseases including cardiovascular disease, gastritis, and gastro-duodenal ulcers (Tanabe et al. 2003). There is also a symbiotic relationship between C. rectus and P. gingivalis, which may provide additional interest in vaccine trials with potentially shared protective outcomes. A relationship between serum titres to HSP70, HSP90, GAD65 (an autoimmune factor in type 1 diabetes mellitus) and serum titres to P. gingivalis has been demonstrated, suggesting that periodontal infection with P. gingivalis may be related to severity of IDDM (Sims et al. 2003).

In immunization studies with DNA fragments of human 60 kDa HSP using the rat model effects, it has been demonstrated that boosting the HSP60 regulatory response may provide an approach to manage human rheumatoid arthritis (Quintana et al. 2003). Studies have identified several T-cell epitopes of P. gingivalis HSP60 (Choi et al. 2004). Further studies identifying cross-reactivity between pathogens associated with periodontitis and other diseases with a potential infectious aetiology may provide avenues for the development of a peptide vaccine strategy not only effective against periodontitis but also against other infectious diseases. Stress protein-derived peptides (HSP60) might provide a significant advantage if they do not induce auto-immune disease while providing immunity to infections of HSP60-carrying bacteria (Amir-Kroll et al. 2003).

Conclusion

The current evidence collected from a large series of diverse and independent studies have clearly demonstrated that active immunization using vaccines against *P. gingivalis* will induce a significant humoral response across animal study models. If passive immunization studies are included, such evidence can also be gathered from human observational studies.

There is sufficient concurring evidence that serum antibodies against *P. gingivalis* antigens are induced by either infection or immunization. There are non-human primate and murine study results with evidence of specific methods to induce an enduring antibody titre without recognizable systemic side-effects. The ambiguity in some study results may depend more on the study model (ligature-induced disease) than vaccine efficacy. High antibody titres appear to provide protection.

Immunization against *P. gingivalis* results in a reduction of the quantity of the target organism in animal models. *P. gingivalis* levels at infected periodontal sites are inversely correlated with antibody titres against the pathogen. Collaborative efforts are needed to ensure successful vaccine development against periodontitis.

References

1. Persson, G.R. (2005), Immune responses and vaccination against periodontal infections. Journal of Clinical Periodontology, 32: 39-53. https://doi.org/10.1111/j.1600-051X.2005.00800.x
2. Bird, P.S., Gemmell, E., Polak, B., Paton, R.G., Sosroseno, W. and Seymour, G.J. (1995), Protective Immunity to Porphyromonas gingivalis Infection in a Murine Model. Journal of Periodontology, 66: 351-362. https://doi.org/10.1902/jop.1995.66.5.351
3. Kudyar N, Dani N, Mahale S. Periodontal vaccine: A dream or reality. J Indian Soc Periodontol. 2011 Apr; 15(2):115-20. doi: 10.4103/0972-124X.84378. PMID: 21976833; PMCID: PMC3183660.
4. Paniker C. K. J. & Ananthanarayan R. (1978). Ananthanarayan and Paniker's textbook of microbiology. Himayatnagar, Hyderabad, Orient Longman.
5. Cruse, Julius M., R. E. Lewis, and Huan Wang. 2004. Immunology guidebook. Amsterdam: Elsevier Academic Press. http://site.ebrary.com/id/10177026.
6. K. D. Tripathi, “Essentials of Medical Pharmacology,” 5th Edition, Jaypee Brothers Medical Publishers (P) LTD, New Delhi, 2003.
7. Edwards C. R. W., Bouchier I. A. D., Haslett C., Chilvers, E. R., & Davidson S. (1995). Davidson's principles and practice of medicine. Edinburgh, Churchill Livingstone.

To cite this article: Periodontal Vaccine: Hiroj Bagde, Nikhat Fatima, Lynn Johnson, Rupma Singh, Rama Univ. J. Dent. Sci. 2022 December; 9 (4): 21-28