JIAPHD

THE JOURNAL OF THE INDIAN ASSOCIATION OF PUBLIC HEALTH DENTISTRY

Vol. 2004 ISSUE : 4

ESTD 1993

"Caries Vaccine" - II. Tomorrow's Reality?

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ABSTRACT

Though the research on caries vaccine started in 1930, much attention has been given to it in the recent three decades. From that time many new vaccines have been developed. The continued research in this field has also disclosed the potential drawbacks. This article explains the recent advances made in vaccine research to overcome the disadvantages of the existing vaccines and future trends that can be considered in the development of a potent vaccine. The article also gives a brief note on the Strain replacement therapy, which could be an immediate solution in the eradication of dental caries.

INTRODUCTION

Although caries vaccine was developed with much anticipation, the results were rather disappointing. However, attempts were constantly made to improve its efficacy. Each new vaccine developed overcame the drawbacks of the previous, but each had its own inherent disadvantage. This article provides an overview of the recent advances that have been tried in caries vaccine production and the alternate to caries vaccine in the form of replacement therapy to eradicate this disease.

RECENT ADVANCES IN CARIES VACCINE PRODUCTION:

1. Sub - unit vaccines
2. DNA Vaccines
3. Adjuvants – with cholera toxin, salmonella toxin
4. Liposomes
5. Biodegradable micro spheres
6. Bio adhesives
7. Plantigens and Plantibodies
8. Advances in route and time of vaccine administration

Sub Unit Vaccines:

Previously, the whole vaccine was introduced into the host to produce an antibody response. This had a potential disadvantage of cross-reaction with heart muscle. To overcome this, Sub unit vaccines are introduced. Here a particular protein antigen of the organism is used as an antigen. Synthetic peptide vaccines based on putative functional domains of glucosyl transferase are developed as sub unit vaccines. They have the advantage of specifically attacking the antigenic surfaces. Antigenic proteins of a different disease causing organism can also be joined together so that, these vaccines can be designed to induce immunity to more than one infection[1].

DNA Vaccines[2]:

The purpose of DNA vaccines is to make the antigenecity more specific and long lasting. The basis for such DNA vaccines is that when a specific DNA is administered into the system, the host can synthesize protein component coded by the DNA. Cell wall protein antigen, of MS is considered a virulence factor because it may mediate initial attachment of the organism to tooth surface. Anti caries DNA vaccine is developed to express cell wall protein.

Lower number of carious lesions and high levels of salivary Ig A & serum Ig G were observed experimental animals following a targeted salivary gland (TSG) administration of this DNA vaccine. However the possibility of the induced DNA to cause damage to the host genetic components has not been completely ruled out. Thus further research is warranted to detect the safety of these vaccines.

Adjuvant:

Adjuvant are molecules to which antigenic peptides are added to achieve a potent immune response. Adjuvant enhances the antigenecity of the antigen by the following ways[3].

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1. It acts as a deposit or reservoir, whereby the antigen can be released progressively.
2. The adjuvant is able to present the antigen directly to the immune competant cells.
3. Some adjuvant acts as chemical immune stimulators of lymphoid cells.

Common adjuvant[4] that has been tried for a long lime are

1. Freund's incomplete Adjuvant- aluminium hydroxide or phosphate.
2. Freund's complete Adjuvant - Freund's incomplete Adjuvant with a suspension of killed tubercle bacilli.
3. Silica particles, Beryllium sulfate
4. Endotoxins

However, important adjuvants used with caries[5] vaccine antigens in the recent research are

1. Mucosal adjuvants e.g. cholera toxin

   A1 subunit of cholera toxin is replaced with chosen protein antigen segment and cholera toxin becomes a chimeric immunogen .
2. Coupling with carrier microparticles
3. Live bacterial vectors eg attenuated Salmonella[6], BCG, normal oral flora

   Oral administration with recombitant-streptococcus lactis IL1403 carrying S.mutans MT8148 surface protein antigen gene has been tried in mice[7].
4. Live viral vectors eg Vaccinia, adenovirus, polio replicons

Thus the addition of adjuvant and antigen together are a significant improvement in the caries vaccination research.

Liposomes:

Liposomes [8,9] (Fig 1) are lipid vesicles lined by external liposomal membranes composed of same lipids as the cell membrane (100nm). Any liposoluble antigen can be incorporated to the lipid membrane and any hydro soluble antigen can be included in the internal cavity of the liposome. Studies in rats show doubling in the efficacy of orally administered vaccine from 40% to 80 % with the use of liposomes.

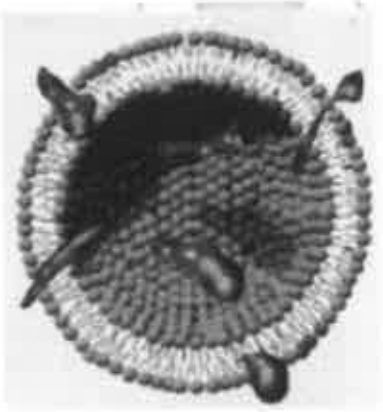

Fig 1. Structure of a liposome

Changing lipid composition can modify particle size of liposomes. A first population of small liposome can deliver the antigen rapidly, while a second population of larger liposome delivers antigen slowly. Thus sustained release of antigen can be achieved.

ISCOM

ISCOM are solid particles generated by combining an antigen with a biocompatible detergent and adjuvant, giving rise to minute structures of 35nm. Protein antigens of caries vaccine can be incorporated in them.

Biodegradable Micro spheres:

Composition of microspheres is similar to surgical sutures. Antigens can be incorporated in to microspheres and released by non-enzymatic rapid hydrolysis. Micro spheres can be placed inside the host tissue and sustained long-term release of antigen can be obtained.

Bio adhesive

Bio adhesive poly D,L – lactide – coglycolide (PLGA) microparticles can also be used to incorporate antigens.

Liposomes, biospheres and bioadhesives have emerged out as effective method to deliver antigen to the host system.

Plantigens and plantibodies

Plants cells have protein synthesis machinery similar to humans. Thus plants can be used to synthesize plantigens (Antigens) and plantibodies (Antibodies).

Researches with transgenic plants started in 1983 with the use of Tobacco plants. Later it was extended in various plants producing fruits and vegetables. Thus eating a transgenic plant derived

fruit (Banana, potato) will not only provide nutrients but also provide protection against infections diseases (Hammond 1999).

CARO Rx ™ [10] is the first clinically tested plantibody. Immediately after professional cleaning of teeth with oral antiseptic solution, CaroRx™ was applied several times over a two-week period. Antibody treatment prevents adhesion of S. mutans to teeth while colonization of other oral bacteria occurs unimpeded. (Fig2) Subjects treated with this, remained caries free for about 6 months in the phase I clinical trials. Phase II clinical trials are in progress now.

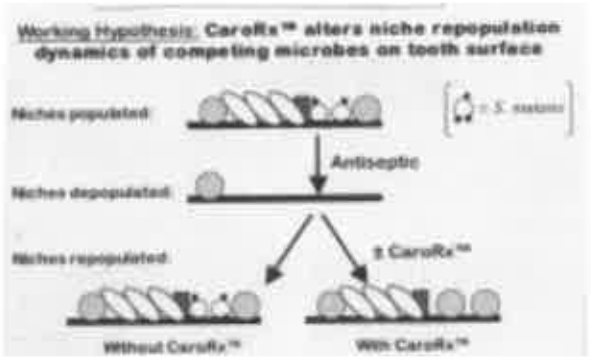

Fig. 2. Working hypothesis of CARO RX™

Advantages are large quantities of antibodies can be derived from plants. The possible transmission of Hepatitis B and HIV by antibody production from animals can be avoided. Incorporating Antibodies in Apples, Banana makes the vaccination procedure feasible and attractive to the general population.

Plantigens have a potential disadvantage of Rhizosecretion[11] of Antigen which may contaminate the soil. Accidental transfer of genes to other plants via pollengrains is also of great concern. [Staub et al 2000]

Advances in Route and time of administration

Previously the exact time at which caries vaccine could be administered remained confusion. Now it is proposed that Caries vaccines are better given at 6 months to one year of age after teeth have begun to emerge but before the mutans streptococci bacteria have begun to colonize[12].

Present studies state that mucosal immunization with antigens (active) administered through oral or intra-nasal routes and passive immunization with topical application and use of transgenic plants can be effective in protection against and eradication of Dental Caries.

Future prespectives

The advances being made in caries vaccine research will definitely lead to the development of a potent vaccine in the near future as a weapon for caries eradication one such discovery that can aid in research is that the transmission of dental caries is more common among the family members. This has been proved by the isolation of a specific strain of organism among family members[13]. Transmission of bacteria to a child mainly occurs from mother. The production of mutacin by S.mutans may help in this transmission[14]. Kohler proposed that reduction of mutans streptococci in pregnant women can lead to reduction in colonization and concomitantly reduced caries in their children. Thus antenatal immunization against caries can be considered.

Caries vaccine is targeted against MS only in the present scenario. But, identification of a conjugate vaccine against all cariogenic oral bacteria may be beneficial in completely eliminating the disease condition.

Periodic administration of caries vaccination like Pulse polio programmes can help in complete eradication of the disease. Extensive research is still in progress to come out with a final effective vaccination for caries.

However, an immediate solution to protect against caries will be the Strain Replacement Therapy.

Strain Replacement Therapy

Strain Replacement Therapy[15,16] is a novel approach to prevent microbial diseases where a harmless effector strain is permanently implanted in the host's microflora. Naturally occurring strain of S. mutans JH1000 has the property to preemptively colonize the human oral cavity and aggressively displace indigenous wild strain by secreting Mutacin 1140, a bacteriocin. Mutacin is an antibacterial substance produced by MS to inhibit the growth of other bacteria.

JH 1140 served as a starting strain for production of effecter strain. From this strain, the entire gene 'ldh' coding for lactate dehydrogenase enzyme is deleted is replaced with alcohol dehydrogenase (ADH).

This genetic remodeling has resulted in an isogenic mutant BCS3-L1 with a significantly

reduced pathogenic potential compared to the original strain. BCS3-L1 has the property of preemptive colonization and Mutacin production without enzymatic activity. Single application of genetically engineered BCS3 – L1 effecter strain should result in permanent implantation of the strain and displacement of pathogenic strain, thus providing excellent protection against Dental Caries.

Hopefully this method can encourage similar efforts to prevent other life threatening infectious diseases.

CONCLUSION

Though caries vaccine and replacement therapy are still in the research state now, they will become a reality in managing, preventing and eradicating this disease. The present day dental practice is mainly concentrated on management of carious lesions. As caries vaccine and caries eradication measures are introduced in the clinical practice, in future, the work of the dentist will transform from caries management to mere caries prevention methods.

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