Novel Researches and Future Aspects of Dental Caries Vaccine: A Literature Review

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ABSTRACT

Current strategies for immunization against dental caries are using the virulence factors of S. mutans as the basic antigen and introducing these antigens into novel mucosal vaccine systems and delivering them with or without adjuvant to mucosal IgA inductive sites. Further advances to make immunization against caries practical will depend upon clinical trials designed to establish whether the findings from animal experiments can be transferred to humans, since most studies are carried out in small animals such as mice. Despite many ongoing laboratory researches, animal studies and clinical trials, none of the universally accepted commercially vaccine has been brought to the market. Understanding the signals for colonization and growth of cariogenic microorganisms in dental biofilms may facilitate us to develop more advanced vaccine strategies that will give long term protective barrier against dental caries and biocompatibility with human race. A review focussing on novel researches and future aspects of caries vaccine is presented in this article.

INTRODUCTION

Dental caries is an irreversible microbial disease of the calcified tissues of the teeth, which is characterized by demineralization of the inorganic portion and destruction of the organic substance of the tooth that often leads to cavitation. It is a multifactorial disease, which is caused by host, agent, and environmental factors.[1-2] Streptococcus mutans (S. mutans), a gram-positive, aciduric and acidogenic bacterium, is regarded as the most significant microorganism associated with dental caries .[3-4] One of the main virulence characteristics of S. mutans is its ability to produce glucosyltransferases (Gtfs), enzymes that synthesize extracellular polysaccharides called glucan, from dietary sucrose. The polymers (polysaccharides) of glucans assist the aggregation of S. mutans to other oral streptococci, apparently through interaction with glucan binding proteins associated with the microorganism cell surface, initiating the biofilm formation. Secretory IgA (SIgA) produced by the mucosal immune system prevents the adhesion of microorganisms to the tooth surface and the onset of bacterial colonization.[5] So, immunization procedures involving the induction of salivary SIgA antibodies can inhibit sucrose-independent/dependent method of streptococci accumulation on tooth surfaces

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and would be an effective mode for inducing caries immunity.

Novel strategies of mucosal immunization have been found to induce high levels of salivary antibodies that can persist for long duration and to establish immune memory.[6] Several studies have been carried out on the development of an efficient vaccine to prevent the occurrence of dental caries. The dental caries vaccine, when it is used in appropriate individuals at an appropriate time, can reduce the recurrence of the disease.[5,6] A review of literature pertaining to novel researches and future aspects of dental caries vaccine is illustrated in this article.

MATERIALS AND METHOD

Search Strategy

A database was created initially with PubMed, focusing on articles published in English language. Articles were searched for caries vaccine, dental caries vaccine. Citations were referenced to identify further relevant articles. Only recent studies focusing on novel researches and future aspects in the field of development of caries vaccine were included.

CARIES VACCINE

Vaccine is an immunobiological matter produced to encourage protection to certain specific disease by stimulating the production of protective antibodies and other mechanisms of the immune system.[5,6] A vaccine is a biological preparation that provides active acquired immunity to a particular disease.[7] Vaccines are produced from live modified organisms, inactivated or killed organisms, extracted cellular fractions, toxoids, or a combination.[6] Developing vaccine for dental caries has been a major goal for many researchers since many years. Caries vaccination is a programmed and planned approach to pre immunized and protect caries prone people primarily children by using proteins present on oral bacterial surfaces mainly S. mutans antigens for inducing human body to produce antibodies against these antigens naturally.[8]

Mechanism of action of dental caries vaccine

Vaccine therapy is done with an objective of preventing infection, i.e., immunization before infection.[9] The objective is that the immunization with S. mutans should induce an immune response, which can prevent the bacterial colonization on the tooth surface, and thus preventing dental caries and the benefit of early immunization might extend until the secondary teeth begin to erupt, exposing new ecological environment.[2,9-10] Studies conducted on the natural history of oral streptococcal acquisition in infants showed that children between 19-31 months often face colonization of S. mutans in their oral cavity under the factors like diet, environment and time. This period is known as Window of Infectivity. Thus, there exists a window of vaccine opportunity between 12th and 18th months.[8] The specific immune defence against cariogenic S. mutans is intervened mostly by salivary S-IgA antibodies.[11] Children between 12 and 24 months demonstrate a wider range of higher concentrations salivary IgA than seen in the first year of life.[12]

Three main groups of antigens (Ags participate in adhesion and accumulation of *Strep mutans* in the biofilm. These Ags are: glucosyl transferases (Gtfs), antigen adhesion I/II (Ag I/II, and glucan-binding proteins (Gbp). The bacterial cell surface protein P1 (also referred to as antigen I/II [Ag I/II], antigen B, or PAc) can mediate the sucrose-independent adherence of S. mutans to the tooth surface. It has been observed that PAc has been used in various experimental methods for inducing specific caries preventing antibodies and inhibiting cariogenic bacterial colonization .[13-14] The glucosyl transferases produce adhesive glucans from dietary sucrose, and the cell-wall-associated glucan- binding proteins have the ability to bind α-1,6-glucan and provide the receptors for glucan-mediated

aggregation. These components can be utilized as main targets for the development of caries vaccines.[2,5,8,10]

Current immunization strategies against dental caries are using the virulence factors of S. mutans as the basic antigen and introducing these antigens into novel mucosal vaccine systems and delivering them with or without an adjuvant to mucosal IgA inductive sites. The most common routes of mucosal immunization are via the oral and nasal route. Mucosal immunization strategies result in the induction of salivary IgA antibody responses**.**[7] A variety of active and passive immunization methods with abundant in vitro and in vivo evidence shows that antibody with specificity for S. mutans adhesins can hinder the bacterial adherence and subsequent caries development.[6]

NOVEL RESEARCHES AND DEVELOPMENT ON ANTI CARIES VACCINE

During the last two decades, several advancements have been done toward the development of a safe caries vaccine for their use in humans. Earlier investigation done on experimental animal demonstrated that salivary IgA antibodies to *S. mutans* were able to protect against caries development led to researches focussing on the immune mechanisms involved in the stimulation and regulation of salivary IgA antibody responses and properties of a vaccine that could be effective in inducing caries immunity and harmless for humans use also.[6]

The cell surface protein called PAc is considered to be a vital preventative target of the virulent factors from S. mutans. The mucosal immunity that only uses soluble proteins or polypeptide antigens cannot produce persistent SIgA.[15] Protein antigens such as PAc alone often produce low immune responses without a potent mucosal vaccine adjuvant. Thus, new mucosal adjuvants have now gained attention for the enhancement of a specific IgA response in oral fluids and for better protection against dental caries.[13]

Liu et al[13] researched for the first time the efficacy of recombinant FimH-S.T, an adhesin component on the tip of type I fimbriae derived from *Salmonella Typhimurium* as a promising mucosal adjuvant for PAc vaccine and found an enhanced PAc-specific antibody response in their study. Shi W et al[16] and Sun Y et al[17] also found enhanced specific IgA responses in oral fluids by directly mixing recombinant mucosal adjuvant flagellin with an antigen or combined with target surface adhesion protein (PAc) in a single fusion protein (KF-rPAc), however Bao et al[18] investigated the therapeutic effect of flagellin-PAc fusion protein (KF-rPAc) against dental caries by using a new immunization protocol on the dental caries development by intranasal immunization in rats with prior implant of *S. mutans* and establishment of carious lesions into their oral cavities.

Yang J et al.[19] administered a second-generation flagellin-rPAc fusion protein, KFD2-rPAc to rats through intranasal immunization and not only found high protective efficiency against caries but also noticed low side effects induced by flagellin .However Jiang et al[20] found enhanced results by addition of the glucosyltransferase-I,(GTF) gene fragment in a dual promoter system in their study. It has been observed that a vaccine, protein p1025 have given away no vacant sites on tooth for S. mutans attachment by occupying all docking sites.[8] Likewise, Calixto GMF et al[21] used peptide p1025 analogous to the fragments 1025-1044 of S. mutans and found that p1025-loaded nanostructured liquid-crystalline system (LCS) presented limited cytotoxicity and also prevented the formation of S. mutans biofilm in their study. Furthermore, Cao et al.[22] produced self-assembled nanoparticles by linking of glucan-binding region of S. mutans glucosyltransferase to the N-terminal domain of ferritin (GLU-FTH) and

found enhanced antibody response and inhibited S. mutans infection in rodents. Batista et al[23] noted antigen-specific antibody production and decline in S. mutans adherence after sublingual administration of $P1_{139—512}$ of S. mutans in combination with the mucosal adjuvant LTK4R (a derivative of heat-labile LT toxin) in mice. Ferreira et al[24] generated a new S. mutans recombinant Phosphate binding-protein (PstS) and observed specific and protective antibody responses after sublingual immunization in mice. Recently, Rather et al[25] found antibodies against purified dextransucrase protein antigen, effectively inhibited the growth of *S. mutans* in their study. Moreover, Yang H et al[11] demonstrated Cold adapted influenza virus (CAIV) by inserting specific antigenic identifier sequences of S. mutans into the viral genome and found it as a promising alternative live vector for an anti caries vaccine.

Additionally, the oral genetically engineered transgenic plants vaccines are observed as the new cost effective concept for advancing modern caries vaccine.[15] Correspondingly, Bai G et al[15] were the first to demonstrate the use of transgenic tomatoes to yield an oral vaccine against S. mutans. In their study, an anti-caries DNA vaccine (PAcA-ctxB) was synthesized by fusing A region of PAc protein-encoding S. mutans gene and cholera toxin B subunit (CTB), a strong immune adjuvant and were transferred to the tomato genomes which provided a useful structure for the development of human caries antigen.

Various laboratory researches and advancements done in the field of dental caries vaccine are presented in Table 1.[11-35] With all these new technologies and increasing knowledge and update, these caries vaccines can be improved further and taken into beneficial human clinical trials.

Table 1: Recent advances and studies done on dental caries vaccine

S. N.	Author	Year	Type of vaccine/ target tissue	Route of immunization /experiment	Efficacy
1.	Rather SA et al[25]	2020	Protein antigen/Purified dextransucrase as the antigen from *S. mutans*.	Immunised subcutaneously, White Rabbits	Antibodies raised against purified dextransucrase effectively inhibited the growth of *S. mutans*.
2.	Yang H et al [11]	2019	Recombinant CAIV with specific antigenic identifier sequences of S. mutans.	Mucosal	CAIV hold a great potential against dental caries.
	Liu ZF et al[13]	2019	Recombinant FimH-S.T protein.	Mucosal, mice	Enhanced specific IgA response.
4.	Bai G et al [15]	2019	A fusion DNA vaccine (PAcA-ctxB) PAc with CTB coding gene.	Integrated in tomatogenomes. (Transgenic tomato plants)	Transgenic tomatoes may provide a useful system for the production of human caries antigen.
5	Yang J et al[19]	2017	Second-generation flagellin-rPAc fusion protein,KFD2-rPAc	Intranasal ,mice	Produces rPAc-specific antibody responses in mice and found KFD2-rPAc as a promising vaccine candidate for caries.

6	Jiang H et al[20]	2017	DNA vaccine with attenuated Salmonella with CMV and nirB promoters	Oral, mice.	This dual-promoter strategy was effective in inducing immune response.
7	Calixto GMF et al[21]	2017	Peptide p1025	Oral, in situ and in vitro	p1025- loaded nanostructured LCS effectively reduced S. mutans biofilm formation.
8	Cao et al[22]	2017	Protein vaccine GLU-FTH were linked	Mucosal, intranasal in rodents	GLU-FTH effectively enhanced antibody production and inhibited S. mutans infection in rodents.
9	Batista et al [23]	2017	P1 protein with LT adjuvant	Sublingual, mice	Shown immune response and reduction in the adherence of S. mutans.
10	Ferreira et al[24]	2016	New protein Pst S	Sublingual immunization ,mice	S. mutans PstS is capable of inducing specific and protective antibody responses.
11	Ren et al [26]	2016	GTFs Protein	Oral, rat model	Compound targeting GTFs was capable to inhibit biofilm formation
12	Colombo NH et al[27]	2016	IgA response S. mutans GbpB.	Saliva collected from Children(36-60 months)	Children with S-ECC have reduced salivary IgA immune response to S. mutans GbpB as compared to caries free.
13	Bachtiar et al[28]	2016	DNA Vaccine	Intramuscular , Hens	Ig Y anti S.mutans ComD reduces biofilm formation.
14	Sun Y et al[29]	2016	Fusion protein (KF-rPAc)	Intranasal immunization, rats	Inhibits biofilm structure formation.
15	Cao et al[30]	2016	PAc and gtfB	3-4 yrs children	No difference in total IgA, anti-PAc s IgA and anti-GLU in children with or without caries
16	Li H et al[31]	2016	DNA Vaccine pVAX1-wapA/ trimethyl chitosan nanoparticles.	Intranasal, rats	WapA resulted in effective anticaries immune response with nanoparticles as an effective delivery system.
17	Bao R et al [18]	2015	Fusion protein (KF-rPAc)	Intranasal, with prior implant of S. mutans into oral cavities of rats.	KF- rPAc could be used as an anticaries therapeutic mucosal vaccine.
18	Batista et al[14]	2014	P1 surface protein	Subcutaneous, mice	Recombinant form of S. mutans P1 surface protein is a potential candidate of anti caries vaccine.
19	Su et al[32]	2014	Vaccine DNA pCI-IL-6	Intranasal, rats	IL6 significantly enhances immunogenicity of anti caries DNA vaccine.
20	Yan HM et al[12]	2013	Protein (salivary IgA enhancement)	Intranasal	Nasal spray significantly enhances IgA and could be

					used as an effective anti caries mucosal vaccine.
21	Chen et al [33]	2013	DNA vaccine	Nasal mucosal route, rat	AL/CA/DNA induces a significant increase in the level of IgA than CS/DNA.
22	Rivera H et al [34]	2013	Peptide antigens from GAS M-surface protein and MuPyV VLPs	Intranasal, mice	MuPyV VLPs induce significant immune response and reduce GAS colonization.
23	Shi W et al[16]	2012	Recombinant FliC as a mucosal adjuvant for anti-caries DNA vaccine.	Intranasal, rats	Could enhance specific IgA responses in saliva and used as an effective mucosal adjuvant for an anti-caries DNA vaccine.
24	Sun Y et al[17]	2012	Recombinant protein KF-rPAc	Intranasal, rats	Flagellin and Pac fusion (KF-rPAc) could be used as an anti-caries mucosal vaccine.
25	Robinette RA et al[35]	2011	Passively administered anti S.mutans monoclonal antibody Guy's 13 plantibody	Mice	Shown humoral response against S. mutans AgI/II (P1).

Cold-adapted influenza viruses (CAIV), Recombinant protein derived from Salmonella Typhimurium (FimH-S.T), A region of cell surface protein PAc (PAcA) coding gene of S.mutans, cholera toxin B subunit coding gene (CTB), Glucan-binding region of S. mutans glucosyl transferase (GLU) ,N-terminal domain of ferritin (FTH), Glucan binding protein S. mutans-(GbpB),Group A streptococcus (GAS), liquid crystalline drug delivery system(LCS),A modular murine polyomavirus (MuPyV) virus-like particle (VLP), Flagellin-PAc fusion protein (KF-rPAc), Cytomegalovirus (CMV), Promoter of the first gene of E. coli NADH-dependent nitrite reductase operon (nirB), *fragment* of the S. mutans wall-associated protein A gene (*wapA)*, Plasmid DNA vaccine vector (pVAX1), Phosphate binding-protein (PstS) ,Plasmid interleukin-6(pCI-IL-6).

FUTURE ASPECTS

Dental caries vaccines would be the first non-living vaccine to be applied by any mucosal route during the first three years of life. Several experimental studies are still being conducted in search of an effective vaccine against dental caries, with favourable future advances in the development of this immunogen. Although many experimental studies done on animal, these results cannot be generalized to humans because of the short time of caries development in the animals and unlike humans, *S.* sobrinus has higher cariogenic potential in these animals than S. mutans. Moreover, rats and mice have different dental morphology and caries standards from humans. For these reasons, studies have been directed in primates, whose immune conditions, etiologic agent and duration of biofilm formation are similar to what occurs in humans.[2] However, further advances to make immunization against caries practical will depend upon clinical trials designed at establishing whether the findings from animal experiments can be transferred to humans, as most studies are carried out in small animals such as mice. [2,5]

Despite laboratory studies with experimental animals, the vaccine production involves large-scale investments that are not feasible and

beneficial for public health systems. This fact marks production relatively unfeasible in the near future, since the dental caries is easily preventable by other simpler and inexpensive means. The most serious hazard is the sera of some patients with rheumatic fever demonstrate a serological cross-reactivity between the heart tissue antigens and certain antigens from haemolytic Streptococci. Polypeptides that are immunologically cross-reactive with the human heart tissue and myosin from muscles of rabbit skeleton are observed in the cell membranes of *S.* mutans and S. ratti. The indications of the colonization and growth of carcinogenic Streptococci in dental biofilms may help us to formulate more refined and informed techniques to "lock out" those bacteria that can cause us harm.[10] Combined efforts should be applied on the most favourable vaccine rather than researchers working in isolation. In animal researches, the outcome procedures such as serum and salivary antibody measurement and their efficacy in inhibiting S. mutans adherence both in vivo and in vitro should be standardized. Caries scores should also be calculated. This will permit comparison of vaccines from various centres. Also, human clinical trials and further studiesh should be conducted to establish efficacy, dosage and the protection time duration as well.[36] However, no vaccines have been taken to market till now primarily due to the low ability to induce and maintain protective antibodies in oral fluids. Regardless of the mechanism through which immune protection against dental caries is attained, few challenges must be overcome through further studies, as the residence time of the vaccine with appropriate concentration in the oral cavity, presence of other microorganisms in caries etiology, best route of administration, reduction in the chance of any antigen cross-reactions and their appropriateness for human use as well.[2,5] More advanced basic research on the mechanism of action of caries vaccine and investigation for some innovative, more effective, and possibly polyvalent vaccines should be performed in the future to fully explore their potential against dental caries.[37]

CONCLUSION

Caries vaccine positively has a role to do in the future as it interferes with the metabolism of the primary pathogen. Numerous new approaches have been tried out to accelate the immune response to achieve a protective effect of caries vaccine. Despite many ongoing laboratory researches, animal studies and clinical trials, none of the universally accepted commercially vaccines that will give long term protective barrier against dental caries and biocompatibility with human race have been brought to the market. Incorporating the dental caries vaccine after its development into public health programs could bring dental caries to a minimal level.

CLINICAL RELEVANCE

Understanding the process of cariogenic S. mutans colonization and growth in dental biofilms may aid in the development of more advanced and beneficial vaccine techniques for public health concern.

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