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Review Article

IMMUNOLOGY OF DENTAL CARIES: A REVIEW

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A B S T R A C T

The mouth is colonized by variety of microorganisms from birth and most of them are commensals, they become pathogenic, when the host responses are altered. The factors which are responsible for maintaining oral health are the integrity of the mucosa, saliva, gingival crevicular fluid and their humoral and cellular immune component. Tissues of the immune system fall into two groups based upon their role inhost defense. Primary (or central) tissues such as immature immune cells, creating andeducating them during their differentiation into mature cells. The bone marrow andthymus are parts of the primary immune system. Secondary (peripheral) immuneorgans look after mature cells that are an active part of defense. It encompasses the rest of theimmune tissues: the spleen, the lymphatic system, lymphnodes and MALT. Of course it is not this simple and the spleen and MALT also help inthe maturation of immune cells.

INTRODUCTION

We live in a potentially hostile world filled with a bewildering array of infectious agents of diverse shape, size, composition and subversive character which would very happily use us as rich sanctuaries for propagating their 'self-genes'. The defense mechanisms which can establish a state of immunity against infection and whose operation provides the basis for the delightful subject called 'Immunology'. Complex network of immune system work together to prevent infection. Different organs and tissues in the body contribute to the function of the immunesystem. These include the circulatory system, bone marrow, thymus, spleen, lymphaticsystem and Mucosal Associated Lymphoid Tissue (MALT). Together these tissues are responsible for the creation, transport and successful operation of mammalianimmunity. Immune responses may be subdivided into two broad divisions, termed *innate* (natural) *immunity* and *adaptive* (acquired) *immunity*. The health of the mouth depends on the integrity of the mucosa which does not normally allow the microorganisms to penetrate[1].

Oral immunology

The mouth is colonized by variety of microorganisms from the time of birth of the baby and through most of them are commensals, they become pathogenic, when the host responses are altered. The factors which are responsible for maintaining oral health are the integrity of the mucosa, saliva, gingival crevicular fluid and their humoral and cellularimmune component.[2].

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Oral immunology is the description of secretory immune system. Oral health depends on the integrity of oral mucosa, which normally prevents the penetration of microorganisms and macromolecules that might be antigenic[3].

Denatl caries

Dental caries is the major problem in the oral cavity. It is the most common infectious disease in man and causes localized destruction of tooth by bacterial action. The main etiological agents of caries are considered to be *Sterptococcus mutants.* Great efforts have been put into studies on immunization against the dental caries. Coming to the etiology, there are three factorsin the dental caries process. Namely, there must bea host or a tooth. Theremust be an agent or a micro-organism that is involved in the caries process, and there must be a substrate or an environment containing appropriate substrates or food which an agent or the microorganism can metabolize to cause dental caries[5].

Local and Systemic Immunity Affecting the Tooth

A remarkable feature of the tooth surface is that it is influenced by, both local salivary and systemic immune mechanisms. The division between the two immune mechanisms occurs near the gingival margin and this is perhaps the only site of the body, where an interphase can be found between the secretory and systemic immune mechanisms. A comparison of the salivary with the gingival domain suggests that, the salivary domain is largely dependent on the function of secretory IgA, the gingival domain is controlled by most, if not all the immune components found in blood. It is evident that the gingival domain is influenced by more versatile and diverse immune mechanisms than the salivary domain. The pulp of the tooth is supplied by the

immune components of the circulating blood and although humoral factors may influence the dentin, it is unlikely that they will reach the tooth surface[6].

Immunology of Dental Caries

Dental caries represents a health expenditure of several billion dollars per year in the world, even though water fluoridation has reduced caries by one half. Thus, although great progress has been made in preventive dentistry, dental caries is still a major health problem, affecting about 50% of children.The National anticaries strategy has been pronged with four goals (1) to combat the microbial agent; (2) to increase tooth resistance; (3) to modify diet; and (4) to deliver anticaries measures to the public. The first goal, combatting the microbial agent, is based on evidence that specific microorganisms are an important part of the pathology of dental caries. Therefore, we can target some, but not all, bacteria for immune regulation.

Role of Innate Factors in Caries

Dental caries is a multifactorial disease, such as; protection againstdental caries involves a number of factors. The teeth are protected by themucosal immune system, but for obvious reasons, some of the cellular components of that system is lacking. Thus, fluid phase factors secreted by salivary glands are thought to be the most important of the mucosal immune components. Persuasively, individuals with salivary hypofunction (especially, xerostomia) often exhibit rampant decay. Although this is usually attributed to water (and quite appropriately so), "nonspecific" innate factors also play a number of functions in protecting the exposed.

Specific Immunity againstDental Caries

Naturally-induced antibodies in children: Infants and young children rapidly develop sIgA antibodies against many oral antigens, presumably by the enterosalivary pathway[7]. Some have observed neither salivary IgA nor crevicularIgG corresponds with colonization by cariogenic bacteria[8] the crevicularIgG antibody is produced locally and appears to reflect caries experience rather than protection. These resultsdo not mean that naturally-induced antibodies are unable to interrupt the caries process.

Caries has been correlated with elevated sIgA antibodies and elevated serum IgM antibodies to *S. mutans.* This probably reflects the elevation of antibody which occurs during and after infections. As such, it is not surprising that it is difficult to make a case for a protective role for antibodies based upon cross-sectional data[9].

Cariesvaccination

In 1924, Clarke isolated an organism that he felt to be from the earliest carious lesions in humans, *Streptococcus mutans.* Although bacteria were widely accepted as the cause of dental caries, it wasn't until 1945-46 that McClure and Hewitt showed that bacteria were indeed potential etiologic agents of dental caries.

Using penicillin, rats, and *Lactobacillus acidophilus,* these workers demonstrated a positive correlation between microbial colonization and dental caries. Subsequently[10] used gnotobiotic rats to prove that ingestion of a cariogenic diet alone was not enough to produce dental caries; and in order for caries to occur, the animals had to be infected by certain bacteria.

By the mid-1960s, the stage was set to combat cariogenic microbes specifically, when a consensus regarding the target organism as well as the target host defense system was reached. After languishing for a decade in the shadows of *Lactobacilli, Streptococcus mutans* re-emerged as the prime candidate for antimicrobial attack as a result of various epidemiological and etiological studies. Thomas B. Tomasi and colleagues in 1965 provided an equally important demonstration that the IgA system was the primary specific immunological element in saliva.

These two advances set the stage for dental vaccination approaches targeting a specific pathogen *(S. mutans)* and manipulating a Specific humoral immune system (sIgA)[9]

Offending Pathogens

Generally, the aim of a vaccine is to reduce the numbers of an offending pathogen or to interfere with its metabolic activity and pathogenic components.

The Lactic Acid Bacteria: Of the lactic acid bacteria, two genera have been associated with caries (because they colonize teeth). These are *Lactobacillus* and *Streptococcus.* The former has been implicated indentinal caries, whereas the latter has been associated with initiating the caries process in enamel.

Criteria for cariogenicity: Focus has been placed upon the lactic acid bacteria as specific etiologic agents initiating dental caries: especially, the "mutans-streptococci," *Streptococcus mutans* and *S. sobrinus).* Cariogenicity cannot be traced to any one property of these streptococci, but rather a combination of biological and biochemical properties. To be cariogenic, anorganism must exhibit tropism for teeth and must be acidogenic and aciduric. Additionally, the organism should utilize refinedsugar (sucrose, a disaccharide of glucose and fructose) as part of the disease process, in view of the direct (albeit, not necessarily linear) correlation between dietary sucrose consumption and caries experience.

Indifferent facultative

In the process of generating energy, indifferent facultative organisms ferment hexoses and always utilize organic acids, as terminal electron acceptors regardless of the presence or absence of oxygen (no oxidative phosphorylation). This is in distinction to true facultative organisms, which utilize oxygen when it is available, forming water and carbon dioxide, rather than acid. Theindifferent facultative organism always produces acid (they areacidogenic). The predominant acid produced by most lactic acid bacteria is lactic acid, which exhibits a lower pKa and less volatility than most organic acids, and is therefore the most destructive to enamel. Lactic acid may also form chelates with Langerhans cells, which would facilitate the dimineralization of enamel [11]

The one other property peculiar to the lactic acid bacteria are their extracellular utilization of sucrose. Species representative of all four genera of the lactic acid bacteria form extracellular glucose polymers (glucans) from sucrose via a glucosyltransferase enzyme system.

Some of the lactic acid bacteria also form polyfructans from sucrose which may also participate in the caries process. There are many species or groups of streptococci inhabiting the mouth and the tooth surface, but the mutans - streptococci have been most closely associated with caries of dental smooth surfaces, pits, and fissures.

In man, the most prevalent serotype of *S. mutans* associated with smooth surface dental caries is serotype c.In smooth surface caries, *S. mutans* serotype cis the predominant group associated with enamel caries[12].

Designing an Anticaries Vaccine

Targetted Immune Systems

Hyperimmunization: The secretory IgA system and the crevicular (serum and gingival) IgG-IgM-IgA system. "Cellular immune" mechanisms were not targeted for several reasons: first, cells would have difficulty functioning in the mouth and second, immunity against bacteria is usually not handled by cellular immune mechanisms unless they are chronic and persistent (usually meaning that the host is having a hard time handling the infection).

Most bacterial infections are handled by secretory immunity (including secretory IgA) or the antibody (IgG)-complement - neutrophil axis. The neutrophil is not always necessary for the latter system to be effective.

Evidence that an anti-caries vaccine would be effective

A number of studies performed in the 1970s indicated that it is possible to protect laboratory animals against dental caries by using hyperimmunization. The results of one of these studies are as follow

Effect of Immunization with S *mutatis* on Caries Scores In Rats

	Mean Caries Score (Some penetration into dentin)		
GROUP	**Buccal**	**Sulcal**	**Proximal**
Immunized and infected	0.6	8.7	0.3
Not immunized and infected	2.1	10.5	16
Not immunized. Not Infected	0.1	1.8	0.0

Michalekefa, 1976. *infect, immun*12:782

Immunization against dental caries starts with the organism most tightly associated with caries, *S.mutans.* Unfortunately, *S.mutant* possesses antigens which are cross-reactive with heart muscle, especially, the cardiolipin of the sarcolemma sheaths. Although patient death is certainly one form of caries control, this means that whole cells of *S. mutans*are not likely to be viewed as acceptable parenteral antigens and they should be used with caution (orally administered).

Therefore, it is of crucial importance to use an alternative means of vaccination. Several alternatives include

1. purification of the candidate antigens and use of a subunit vaccine
2. Using recombinant DNA methods to place virulence factors from cariogenic organisms into a non-cariogenic, non-cross reactive bacterium.

Candidate antigens have been selected because they are believed to play some role in the pathogenic activities of *S. mutans* and *S. sobrinus.* Extracellular protein targets include glucosyltransferases (GTF), dextranases, adhesins (such as Spa A or SA I/II), and glucan-binding protein. Other nonprotein candidate antigens have also been proposed, including extracellular glucans and the serotype-defining antigen.

Routes of Vaccination

Currently, there are two favored potential routes of vaccine administration: Perioral and Intranasal (nasal) [13]. Whole cells of *S. mutans*encapsulated withingelatin were used to immunize human volunteers. The question waswhether slgA antibodies can be elicited by oral ingestion of whole *S.mutans. A priori,* this form of vaccination requires the activity of the"enteric pathway," since gelatin capsules preclude intraoralimmunization. It has been reported that peri-oral immunization by *S.mutans* can elevate sIgA antibodies (Gregory and Filler. 1987)**[9].** Individuals were administered gelatin-capsules (10 consecutive days) containing killed *S. mutans*whole cells which was isolated from thevolunteer themselves. SIgA, specific against GTF and SA I/II were detected in all cases, and in each case, there was a reduction in viable *S.mutans* isolated from dental plaque, but it was unclear whether this wasof any value in terms of caries prevention. SIgA antibodies were detected in the saliva and tears, and in the colostrum/milk of mothers giving birth. The question which was not addressed was whether, potentially harmful serum IgG antibody against LTA was elicited by this protocol. Further, other studies suggest that peri-oral immunization is not always this successful[14].

Synthetic: Peptide Vaccines

As indicated above, at least two regions of the Agl/II-protein family appear to beassociated with salivary-binding functions. Monoclonal antibody, raised by immunizationwith intact Ag *I/II* that reacted with the fragment containing the proline-rich region inhibited the formation of experimental dental caries. Similarly, workers in francedemonstrated that a 14-mer peptide derived from a proline-rich region ofreactive with member of the S. mutans serotype of Ag I/II family of proteins, antibody to the native protein. Synthetic peptide approaches have also shown the alanineric repeat region of Ag I/II to be immunogenic and to induce protective immunity. For example, subcutaneous immunization with a synthetic peptide derived from the alanine rich region of Ag I/II from S. mutans (residues 301-319: PAcA) induced higher levels of serum IgG antibody reactive with recombinant Ag I/II than a synthetic peptide derived from the proline-rich region (residues 601-629).Intranasal immunization with PAcA, coupled to cholera toxin B subunit, suppressed colonization of mouse teeth by S. mutans. Fusion proteins containing PAcA also inhibited sucrose-independent adhesion of S. mutans to saliva-coated hydroxyapatite beads. Thus, this S. mutansadhesin contains multiple functionally based epitopes that are sufficiently immunogenic to be considered for dental caries vaccines. B- and T-cell epitopes have been found in a cell-associated 3.8-kDa protein component antigen[7].

Lehner and his colleagues (Lehner*et al*, 1989) applied free synthetic peptides containing immunodominant sequences of the 3.8-kDa antigen of S. mutans to the gingival mucosa of macaques, resulting in the formation of both salivary IgA and gingival IgG antibody. Anti-peptide antibody elicited by this topical application method prevented colonization of the teeth by S. mutans. The identification of functionally relevant residues domains in glucosyltransferases has led to the design of several synthetic peptide vaccines. Monoclonal or polyclonal antibody preparations which were directed to one of several N-terminal GTF peptides each of which contained different catalytically implicated residues, have been shown to inhibit GTF activity. Several of these synthetic peptides which contained strong B-cell epitopes were synthesized on lysine backbones to contain four or eight copies of the respective

sequence. These constructs induced protective immunity against experimental dental caries.

Synthetic peptide constructs have also been based on sequence derived from the repeating sequences in the C-terminal' third of GTF, which has been shown to be associated with primer-dependent glucan binding. A synthetic peptide associated with a putative glucan-binding site contains both B- and T-cell epitopes, to induce antibody which could inhibit the enzymatic activity of GTF, and to induce protective immune responses in the rat caries model[15].

Furthermore, di-epitopic constructs of this peptide and a peptide from the catalytic domain could be shown to enhance the protective effect, presumably because antibody was raised to two functional targets and because the glucan-binding domain peptide provided additional T-cell help for the B-cell epitopes on both peptides. All of the GTF synthetic peptide sequences which showed protective effects in the above experiments are highly conserved among S. mutans and often among S. sobrinus GTFs as well. Antibody directed to these epitopes could therefore be expected to reduce the activity of many of the GTF iso-enzymes expressed by these mutans streptococci, thus extending the protective effect across species lines. In this regard, protection from dental caries caused by either S. mutans or S. sobrinus infection in the rat model has been demonstrated after immunization with synthetic peptides from either the catalytic or glucan-binding domains of one GTF isozyme. These studies suggested that protection could be achieved by immunization with discrete epitopes associated with several virulence characteristics. Combining epitopes from adhesins and GTFs into one construct and enhancing the immune response with additional sequences *(e.g.,* cholera toxin subunits) could theoretically increase and possibly extend the protective effect of these subunit vaccines. Some recombinant protein approaches, described, have used this design[14].

Recombinant vaccines

Attenuated expression vectors

Recombinant approaches afford the expression of larger portions of functional domains that can be accommodated by synthetic peptides. Also, gene fusions of a functionally relevant sequence linked to a mucosal adjuvant sequence can result in chimeric proteins inherently able to enhance immune responses to the functional epitopes. Furthermore, attenuated mutant vectors such as Salmonella, which contain plasmids expressing recombinant peptides, can target the vaccine to appropriate inductive lymphoid tissue for mucosal responses. Several of these approaches have successfully induced protective immune responses for experimental dental caries in rats or mice by means of chimeric proteins or vectors expressing either adhesin or GTF epitope[14].

Redman and co-workers have shown (1994, 1995) that oral immunization with recombinant Salmonella typhimurium, expressing surface protein antigen A of Streptococcus sobrinus, was able to induce persistent mucosal immune responses this could confer protection after challenge of Fischer rats with cariogenic S. sobrinus[14].

Hajishengallis and co-workers (1992)[16] have genetically linked the 42-kDa salivary binding receptor (SBR) of S. mutans Ag I/II with the A2 and B subunits of cholera toxin (SBR-CTA2/B) and expressed this chimeric protein in E. coli BL21. Intranasal administration of this chimeric protein with CT resulted in significant reductions in dental caries caused by infection of Fischer rats with S. mutans UA130. The SBR-CTA2/B, expressed in an attenuated S.typhimurium BRD509 vaccine strain containing anirB promoter, which was administered intranasally or intragastrically to antibiotic-pre-treated BALB/c mice, resulted in salivary antibody to the SBR and a significant reduction in the number of S. mutans PC3379 recovered from dental plaque after challenge.

Jespersgaard and co-workers (1999) intranasally immunized BALB/c mice with an E. coli expressed recombinant GTF peptide based on a 290-residue glucan-binding domain sequence, or with a chimeric protein combining this sequence with thioredoxin. Immunization with either peptide resulted in protective effects on experimental S.mutans infection and on resulting dental caries. Other recombinant strategies involving either adhesin or GTF constructs, with or without mucosal adjuvant sequences, have been shown to induce immune responses to these functional domains which could be ultimately protective in caries vaccine applications. Chimeric proteins, in which short sequences from predicted catalytically active regions of GTF were combined with cholera toxin or the B subunit of CT and expressed in E. coli HB101, gave rise to immune responses which could inhibit as much as 50% of GTFB activity[14].

Yu and coworkers (1997) designed a fusion protein which contained both a 281 residue saliva-binding alanine-rich region of S. mutans Ag I/II and a 392-residue glucan-binding domain of GTF-I. A recombinant fusion protein, expressed in E. coli XLl-Blue, induced IgG antibody in rabbits or in Holstein cows which could inhibit glucan synthesis by GTF and sucrose-independent and -dependent adhesion of S. mutans to saliva-coated hydroxyapatite beads. Constructs involving the attenuated human S. typhi vector would be expected to have more potential for human vaccine applications than would S. typhimurium, which is a murine pathogen. In this regard, attenuated S. typhi CVD908 strains have been prepared to express peptide chimeras in which GTF sequences, associated with the glucan-binding domain, are combined with tetanus toxin fragment C for immunogenicity[14].

Conjugate Vaccines

Another vaccine approach which may intercept more than one aspect of mutansstreptococcal molecular pathogenesis is the chemical conjugation of functionally associated protein/peptide components with bacterial polysaccharides. Added to the value of including multiple targets within the vaccine is that the conjugation of protein with polysaccharide enhances the immunogenicity of the T-cell-independent polysaccharide entity.

This principle was first demonstrated by[17] and Avery and Goebel (1929) and has been applied with great success in the Hemophilusinfluenzae type b conjugate vaccines to induce protective immunity to the capsular polysaccharide of H. influenzae in infants and young children. Two groups have applied this approach to dentally relevant components**.** Lett and co-workers (1994)[18] covalently coupled an adhesin-associated 14 mer synthetic peptide to the serogroup f polysaccharide of S.mutans strain OMZ 175 by reductive amination. Subcutaneous injection with the conjugate induced systemic IgMand IgG antibody responses to both peptide and

polysaccharide which could be boosted upon subsequent injection.

The presence of both B- and T-epitopes in the peptide was required for effective responses. Intragastric intubation of the conjugates associated with liposomes induced primary and secondary salivary IgA antibody to both components. In separate studies, have reported that conjugation of either tetanus toxoid or S. sobrinm GTF to the water-soluble glucan synthesized by GTF significantly enhanced serum IgG and salivary IgA antibody levels to the water-soluble glucan and to the conjugated protein. Serum GTF inhibitory activity was also improved by conjugation. The relative protective capacity of either conjugate approach has yet to be tested. Since initial S.mutans infection occurs at an age (< 2 yrs) when children are unable to mount significant anti-polysaccharide responses, these approaches will be especially important if conjugate vaccines are shown to enhance the level of protection significantly over that achieved with protein-based vaccines[14].

Molecular Genetics and the Enteric Pathway

Molecular genetics approaches now offer one of the most exciting means of delivering a "subunit" vaccine which would be cost effective. The problem with subunit vaccines has been the inability to maintain sufficiently high levels of antigen in the gut to stimulate antibody production in a cost-effective manner. Recently, candidate antigen genes have been introduced into "harmless" enteric bacteria. These bacteria proliferate for some time and exhibit considerable greater staying power in the gut than simple gelatin capsules filled with antigen. This method of immunization is currently under investigation. But think about it, no microbe which can colonize a human should be considered totally"harmless." Also, some of the plasmid vectors used are marked with genes encoding antibiotic resistance[15].

Gingival swabs and the local pathway

The gingiva is an area in which local immune responses can be elicited. The swabbing of gingiva with a 3800 kd low molecular weight component of *S. mutans*has been found to elicit both increases in IgG in the crevicular fluid and sIgA in the saliva of monkeys (Lehner*et al,* 1986).

From this point, it is difficult to ascribe the sIgAresponse to local (gingival) immunization rather than the enteric pathway, since some antigen must be ingested. From a therapeutic point of view, the method itself may be useful: ie, the swabbing was administered only ten times over a year period and resulted in a reduction in *S. mutans*as well as caries.

Liposomes

Liposomes are artificial membrane vesicles which can be prepared to contain both aqueous-phase solutes internally or intramembranous molecules within their membranes. Liposomes represent a relatively benign mechanism of increasing immune responsesto antigens (ie., they are "adjuvants"). One method of increasing antibody responses by gingival immunization has been the sequestration of candidate antigens (GTF, in this case) into liposomes, permitting the liposomes to dessicate, and administering the dehydrated liposomes to humans. This resulted in salivary IgA2 antibodies against GTF, suggesting that dehydrated liposomes may be useful in generating specific salivary immunity against target antigens in the oral cavity[19]

Coupling

Another method for enhancing immune responses to antigens is to couple the "poor"antigen to a "good" antigen. For example, polysaccharide antigens are usually poor antigens: they tend to be independent and therefore, sustain primary immune response characteristics (without T-cell, it is difficult to get isotype switching or hypermutation). To circumvent this problem, polysaccharide antigens may be coupled to a protein (proteins are T-dependent, usually). This will result in increased specificity and isotype switching. Intragastric administration of liposomes containing polysaccharides of *S. mutans* coupled to a protein has been used in the rat[20].

Antiidiotype vaccine

One potential method for eliciting antibodies against any target includes the use of an antiidiotypic vaccine. In this approach, antibodies which possess an idiotope that resemble a bacterial epitope (ie. "internal image" antibodies) are injected into a host. If these antibodies are the same allotype as the host, the host will form antibodies against only the internal image. These antibodies against the internal image can then stimulate antiidiotypic antibodies which also can bind to bacteria[20]. Interestingly, the study cited also used liposomes as a mechanism of delivery of the antiidiotypic antibodies by gastric intubation. The antiidiotypic vaccine leads to greatly reduced caries in the gnotobiotic rat model.

Adjuvants

Many of the peptide antigens described above would be poorly immunogenic where it not for the use of adjuvants. The dentist should be aware that many traditional adjuvants used in animals (such as complete Freund's adjuvant, a mixture of mycobacterial components and mineral oil) are too toxic for human use. An inexpensive adjuvant approved for use in humans is "alum," an inorganic salt of aluminum. Liposomes, mentioned above, may offer an attractive adjuvant system. The most promising adjuvant stimulating mucosal sIgA responses appears to be cholera toxin, which is under intense investigation by Michael Russell's group at the University of Alabama. It appears to stimulate persistently high levels of sIgA after a single boost[16]. Cholera toxin is a heterodimer featuring atoxic CTA-subunit and anontoxic CTB-subunit. Adjuvanticity isassociated with the nontoxic CTB subunit, and a clever approach has been to replace the CTA-subunit with antigens-such as SA I/II — derived from S". *mutans*[21]. And indeed, as you may have predicted, they have even constructed an enteric bacterial clone which expresses SAI/II-CTA2/CTB. The enteric bacterium selected for this was an 'avirulent' strain of *Salmonella typhimurium* (Harokopakis*et al*, 1997*)*

Potential for aPassive Immunization Approach

When antibodies are passively administered to monoinfectedgnotobiotic animals, as expected, a reduction in disease occurs. Monoclonal antibodies against *S. mutans*can also prevent the colonization of human teeth by *S, mutans*(Ma *et al,* 1987)[22]. Thus, passive immune approaches may reasonably be expected to be effective. However, "cost effectiveness" is another issue. Dental scientists have developed a number of fairly clever stratergies which may see future application.

Maternal Immunization

Passive immunization can occur by oral immunization (secretory IgA is stimulated) of pregnant rats. The milk from immunized rat mothers confers protection to the weanlings. It is possible that any mammal can be protected in this fashion.

XenogeneicImmunization

It has been shown that cows can be immunized against cariogenic bacteria and that antibodies against those bacteria appear in the cow's milk.

The cow's milk can then confer protection immunity in a passive manner. This type of immunization is shown in the diagram. The antibodies were of the IgGl subclass, indicative of the parenteral immunization used. In cow's milk and colostrum, IgGl is the major secreted immunoglobulin isotype. Both *S. mutans* and caries scores were reduced (Michalek *et al*,1987)[23] in gnotobiotic rats. Of course, gnotobiotic rats are easy to protect compared to conventional animals and humans; however, from immunized cows, used as a mouthrinse, appeared to decrease *S. mutans* in volunteers.

Past, Present, and Future Human Applications

Active immunization

Few clinical trials have been performed to examine the protectiveeffect of active immunization with dental caries vaccines containingdefined antigens. However, several studies have shown that mucosal exposure of humansto immunization with glucosyltransferases from S. mutans or S. sobrinus can lead to theformation of salivary IgA antibody, albeit at modest levels. Childers and co-workers(1996)[19] orally immunized adults using enteric-coated capsules filled with crude S. mutansGS-5 GTF antigen preparations contained in liposomes. Parotid salivary IgA antibody responses, primarily of the IgA2 subclass, were induced in five of seven subjects. Similarly, nasal immunization with dehydrated liposomes containing this GTFpreparation induced significant IgA 1 antibody response in nasal washes. Parotid salivary antibody levels to GTF were of lower magnitude. In earlier studies, this group showed that oral administration of capsules containing the purified serotype carbohydrate antigen of S. mutans in liposomes gave rise to low but detectable levels of salivary antibody.

Smith and Taubman (1987, 1990)[7] reported that mucosal immunization with GTF could influence the re-emergence of mutans streptococci in young adults after a dental prophylaxis. Levels of parotid salivary IgA antibody to GTF increased after oral immunization with S. sobrinus GTF in enteric capsules, administered together with aluminum phosphate. Immunization under this protocol delayed the re-accumulation of indigenous oral mutans streptococci, compared with a placebo group given buffer-filled capsules. A delay in mutans streptococcal re-emergence was also observed after topical administration of GTF on the lower lip, although this protocol did not result in a significant detectable increase in antibody to the vaccine. Taken together, these studies support the hypothesis that mucosa. Immunization with dental caries vaccines could be protective, especially in pediatric populations where mutans streptococci are not yet a permanent member of the dental biofilm.

Passive Immune Approaches

Passive antibody administration has also been examined for effects on indigenous mutansstreptococci. Mouthrinses containing bovine milk or hen egg yolk IgY antibody to S. mutans cells led to modest short-term decreases in the numbers of indigenous mutansstreptococci in saliva or dental plaque. Long-term effects on indigenousobserved after topical application of mouse monoclonal IgG or transgenic plant secretorysIgA/G antibody, each with specificity for Ag I/II. Inthese experiments, teeth were first treated for nine days with chlorhexidine. Following anti-bacterial treatment, antibody was topically applied for three weeks. Recolonization with mutans streptococci did not occur for at least two years after treatment of subject with mouse monoclonal antibody or at least 4 months after treatment with the transgenic antibody to the Ag I/II epitope. In contrast, the teeth of all subjects topically treated with nonspecific monoclones were re-colonized with mutans streptococci by 82 days in the former experiment and by 58 days in the later experiment. The authors suggest that the secretory form of the monoclonal antibody may be more efficacious because of its apparent increased survival time in the oral cavity, compared with IgG, as well as the increased avidity emanating from itstetravalency. The explanation for the long-term effects on mutans streptococcal colonization after a relatively short exposure to antibody remains unresolved. Thus, topical or dietary administration immune reagents with specificity for epitopes on these proteins may also have potentialhuman application.[24]

Prospects and Concerns

Traditional vaccine therapy indicates that immunization should take place prior to infection. Given the apparent pattern of mutans streptococcal colonization and the association of these organisms with disease, this would suggest mat immunization for dental caries should begin early in the second year of life for those populations under normal risk for infection **(**Toshihiko Koga 2002).[25]

If we accept that each approach couldgive a reasonable level of protection in humans, one still needs to consider for whom and under what circumstances the dental caries vaccine is intended. For example, the idealvaccine application for a child with asthma, the second most common chronic childhoodailment, may be at a site *(e.g.,* rectal) and with an adjuvant (e.g., detoxified CT or LT) mat is quite different from that sufficient to give a protective response *(eg.*intranasal) to a healthy child.

Also, from economic and societal standpoints, a vaccine strategy forchildren to whom the full advantages of pediatric care are available may not be the idealapproach for children with limited health care access.

Since the thrust of the WHO vaccine effort is to reduce, rather thanincrease, the number of different immunizations that a child receives, an approach thatcombines epitopes from several vaccines is likely to be perceived as more desirable forglobal application.

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