CARIES VACCINE

Concept of vaccination against caries has existed almost from time that this disease was recognized to result from colonization of teeth by acidogenic bacteria, even though etiological agents were originally thought to be lactobacilli. Given general appreciation for infectious component of dental caries, injected vaccines containing lactobacilli were administered with limited success in the 1940s. However, at that time molecular pathogenesis of S. mutans was unknown, nor was there an understanding of immune mechanisms that operate in oral cavity. Most virulence characteristics were unclear, with exception of ability of cariogenic bacteria to produce enamel-dissolving acid. Modern era of vaccine therapy began in late 1960s with William Bowen’s use of S. Mutans to intravenously immunize irus monkeys.Today we have answered many of these questions, permitting us to more knowledgeably explore potential for vaccine therapy for dental caries associated with S. mutans.Acquisition of MutansStreptococciLandmark experiments in 1960s (reviewed in Gibbons & van Houte, 1975; Loesche, 1986) established that mutans streptococci are primary etiologic agents of this disease & that infection is transmissible. Strong association exists b/n level of colonization with mutans streptococci & caries, although other organisms, such as lactobacilli, have also been implicated in this disease. Under normal circumstances of diet & challenge, children become permanently colonized with mutans streptococci b/n middle of 2nd year & end of 3rd year of life, during a so-called “window of infectivity” (Caufield et al., 1993).Many studies have shown that primary source of infection is maternal, although there is recent evidence to suggest that non-familial transfer can occur when environmental conditions favor colonization (Mattos- Graner et al., 2001).Infection is related to maternal dose (Kohler et al., 1984; Caufield et al., 1993), in that higher level of maternal mutans streptococcal infection, higher % of children who become infected. If environment strongly favors mutans colonization —for Ex, if high maternal infection levels are combined with high dietary sucrose levels—this so-called “window of infection” shifts to an earlier age. Many have also suggested that mutans streptococci can be found in oral cavity during 1ST year of life, especially in caries prone populations (Milgrom et al., 2000). However, despite influence of maternal dose, children who do not become infected by # 3 years of age appear to remain uninfected, or minimally colonized for several years (Caufield et al., 1993; Smith et al., 1998a), possibly until new opportunities for colonization occur upon eruption secondary dentition. This suggests that longer-term benefit could ensue if mutans streptococcal colonization could be impeded in early childhood by measures such as immunization. Ontogeny of Immunity in SalivaImmunological interception of initial attempts of mutans streptococci to colonize tooth surface would seem to be preferred vaccine strategy since these organisms are exceedingly difficult to displace once they become part of dental biofilm.Given natural history of mutans streptococcal infection, this strategy would require year old children to be sufficiently mature immunologically to form protective levels of antibody in their oral cavity at this time. Secretory IgA (SIgA) is principal immune component of major & minor gland salivary secretions & thus would be considered to be primary mediator of immunity. Although SIgA antibody in saliva & other secretions is essentially absent at birth, mature SIgA—is principal salivary immunoglobulin secreted by 1 month of age. Induced by Environmental antigenic challenge, mucosal IgA antibody to pioneer oral microbiota appears in secretions within weeks of initial microbial exposure.By 6 to 9 months of age most children exhibit an adult like distribution of salivary IgA subclasses, which include antibody to several antigens of predominant pioneer oral flora.Can children respond to natural exposure to mutans streptococci ?The answer is yes Salivary antibody to mutans streptococcal antigens is usually 1ST observed in 2nd & 3rd years of life. Salivary responses are often directed to those streptococcal components that are important in colonization & accumulation, such as antigen I/II, GTFs, and GBPs. Longitudinal studies suggest that these antibody specificities result from contact with mutans streptococci. Interestingly, in some children, antibody to mutans streptococcal antigens can also be detected independently of ability to detect ongoing infection in 2nd year of life. Most children apparently respond immunologically to transient infection or ongoing colonization with mutans streptococci in early childhood. Although distribution & specificity of children’s responses are not identical, antibody to a few major antigens predominates. These data suggest possibility that such responses could be protective if induced prior to critical colonization events.MOLECULAR PATHOGENESISThirty years ago British & American scientists demonstrated that experimental protection could be achieved by immunization with mutans streptococci (reviewed by Michalek and Childers7). Attention then focused on immunologically intercepting properties of these organisms that led to disease. Molecular pathogenesis of mutans streptococci involves several phases, each of which offers targets for immunological intervention.Initial attachment to tooth occurs by interaction of bacterial proteins i.e adhesins with lectins in dental pellicle covering tooth surface. These bacterial adhesins, first described by Russell & Lehner is referred as antigen I/II.bacterial adhesins binds to glycoproteins found in salivary pellicles that coat tooth surface In presence of dietary sucrose, GTFs synthesize e/c glucans. glucans provide scaffolding for aggregation of mutans through interaction with bacterial cell-associated glucan-binding proteins . GTFs also contain glucan-binding domains. Theoretically, next phase of pathogenesis results from metabolic activities of these masses of accumulated mutans streptococci. Mutans streptococci are most prolific producers of lactic acid in these accumulations although other “low pH bacteria” may also contribute. Dental caries ultimately ensues because resulting increase in lactic acid concentration cannot be sufficiently buffered to prevent enamel dissolution. Effective Molecular Targets for Dental Caries VaccinesSeveral stages in molecular pathogenesis of dental caries are susceptible to immune intervention. Microorganisms can be cleared from oral cavity while still in salivary phase by antibody-mediated aggregation. Antibody could also block receptors necessary for - colonization (e.g., adhesins)/ - accumulation (glucan-binding domain of GBPs & GTF) 3. Immune inactivation of GTF enzymes - prevent formation of glucan matrix. Most of recent experimental effort has been directed toward ADHESINS, GTFS, & GBPS as vaccine targets.(A) ADHESINSAdhesins from 2 principal human pathogens, Streptococcus mutans (identified as antigen I/II, PAc, or P1) Streptococcus sobrinus (SpaA or PAg), have been purified. Russell and Lehner initially described S. mutans component in 1978. Antigen I/II was found both in culture supernatant as well as on S. mutans cell surface. . Significant sequence homology (66%) exists b/n S. mutans AgI/II & S. sobrinus SpaA (Tokuda et al., 1990: LaPolla et,al 1991) However, despite homology b/n 2 mutans streptococcal adhesins, each appears to bind to separate components in pellicle Abundant in vitro & in vivo evidence indicates that antibody with specificity for S. mutans AgI/II or S. sobrinus SpaA can interfere with bacterial adherence & subsequent caries. Numerous immunization approaches have shown that active immunization with intact antigen I/II or passive immunization with monoclonal antibody (Ma et al., 1990) can protect rodents, primates, or humans from caries caused by S. mutans. Immunization of mice with synthetic peptide of antigen I/II suppressed tooth colonization with S. mutans (Takahashi et al., 1991). Immunization with S. sobrinus SpaA constructs protected rats from caries caused by S. sobrinus infection (Redman et al., 1995). Protection in these experiments could conceivably occur by antibody blockade of initial colonization events or antibody-mediated agglutination & clearing of adhesin-bearing bacteria from saliva.(B) GLUCOSYLTRANSFERASES (GTFs)S. mutans & S. sobrinus each synthesize several GTFs- considerable sequence homology. Genes responsible for glucan synthesis in S. mutans are gtfB (Shiroza et al., 1987), gtfC (Pucci et al., 1987), & gtfD (Honda et al., 1990)Genes responsible for glucan synthesis in S. sobrinus are gtfI (Russell et al., 1987) and gtfS (Gilmore et al., 1990).Mutans streptococci that have lost ability to make glucan in GTF genes do not produce significant disease in animal models. Growth of mutans streptococci in presence of antibody to GTF significantly diminishes amount of biofilm on glass surfaces. Thus it was not surprising that immunization studies using intact GTF vaccines successfully protected animals infected with S. mutans. Since mutans streptococcal GTFs bear significant homology, active immunization with either S. mutans or S. sobrinus GTFs induced protective immune responses in experimental dental caries rodent models after infection with several mutans streptococcal species (reviewed in Smith and Taubman, 1997). Passive administration of antibody to GTF in diet also can protect rats from experimental caries (Hamada et al., 1991). Thus, presence of antibody to glucosyltransferase in oral cavity prior to infection can significantly influence disease outcome.(C) Glucan-binding proteins.Since glucan-binding proteins on surface of mutans streptococcal cells may provide receptors for glucan-mediated aggregation, these proteins have also received attention as vaccines. Many proteins with glucan-binding properties have been identified in Streptococcus mutans & Streptococcus sobrinus (summarized in Smith et al., 1998b). S. mutans secretes at least 3 distinct proteins with glucan-binding activity: GbpA (Russell, 1979), GbpB (Smith et al., 1994a), and GbpC (Sato et al., 1997). Of 3 S. mutans glucan-binding approaches only GbpB has been shown to induce protective immune responses to experimental caries. (Smith et al., 1997aBiofilm formation on plastic surfaces by strains of S. mutans is directly correlated with expression of GbpB (Mattos-Graner et al., 2001), suggesting role for GbpB in this process. Protection can be achieved by either subcutaneous injection of GbpB in salivary gland region (Smith and Taubman, 1996) or by mucosal application by intranasal route (Smith et al., 1997a). Saliva samples from young children often contain IgA antibody to GbpB, indicating that initial infection with S. mutans can lead to natural induction of immunity to this protein (Smith et al., 1998a). protection induced by S. mutans GbpB does not extend to S. sobrinus species.