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Gonococcal Vaccines

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The quest for a vaccine against *Neisseria gonorrhoeae* has been long, arduous, and, to date, unsuccessful. Indeed, some experts, citing the recurrent nature of gonococcal infections in some people, have believed the task to be impossible (2).

However, there has been at least one human challenge study that has demonstrated protection against the homologous infecting organism after immunization with purified gonococcal pili (4). Furthermore, *N. gonorrhoeae* is quite antigenic for humans, local and systemic immune responses have been demonstrated against virtually every gonococcal antigen studied, and relative resistance to infection has been correlated with a history of previous infections (22).

PATHOGENESIS

An understanding of the basis for a vaccine requires a working knowledge of the pathogenesis of the infection. The pathogenesis of a gonococcal infection can be broken down into five stages: (i) distant attachment, mediated by pili and perhaps pilus-associated proteins; (ii) close attachment, mediated primarily by cell wall protein antigens and perhaps lipooligosaccharides (LOS); (iii) ingestion by mucus secretory cells, which is mediated at least in part by protein I; (iv) transportation through the cell body in phagosomes, a host cell function; and (v) egestion through the basement membrane (although the proof for this last step is not absolute).

A variety of different immunological tests have repeatedly demonstrated the following: (i) a human antibody response is invoked by a gonococcal infection; (ii) the magnitude, antibody isotype, and antibody specificity of the response are unpredictable but tend to be more pronounced in women; (iii) there is a significant amount of cross-reactivity with antibody induced by other organisms; and, most importantly, (iv) to date, no correlation of the type or level of antibody has been made with protection. Local antibody, which functions primarily by blocking attachment of gonococci to eucaryotic cells, is present but at a reduced level (50).

ANIMAL MODEL AND IN VITRO CORRELATES WITH IMMUNITY

There is no animal model that correlates with the human infection. Thus, meaningful infection can be carried out only in the natural host, the human.

Without a relevant animal model, an in vitro correlate of immunity could serve as a guide (e.g., serum bactericidal antibodies served as the relevant in vitro correlate for the development of the successful meningococcal vaccine). Unfortunately, an in vitro correlate of human immunity has not yet been found. Thus, experimental studies in human volunteers and field trials must be relied upon if we are to fully understand the pathogenesis of gonococcal infections and to test the utility of vaccine candidates.

HUMAN VACCINE CHALLENGE STUDIES AND TRIALS

A number of vaccines have been studied in the past. In this brief review, however, only the most recent vaccine preparations will be discussed.

On the basis of (i) the demonstration that piliated gonococci are the most pathogenic for humans (17, 18), (ii) the successful human challenge study with a gonococcal pilus vaccine derived from the challenge organism (4), (iii) the demonstration of a consistent immune response following immunization (51), including the production of local antibody (24), and (iv) the suggestion that the pilus vaccine preparation might be broadly cross-reactive (51), a large gonococcal pilus vaccine trial involving 3,250 volunteers was undertaken in 1983. No overall protection was detected, although a significant proportion of the volunteers developed an antibody response (49). Therefore, a gonococcal pilus vaccine made up of the entire pilus derived by mechanical shearing and then purified by physico chemical means is unlikely as a potential vaccine candidate.

A protein I vaccine challenge study has also been conducted (E. W. Hook III, personal communication). The vaccine derived by differential centrifugation of disrupted gonococci was more than 85% pure for protein I. It was well tolerated, a significant antibody response was elicited, but it afforded no protection against an intraurethral challenge in men with the homologous organism.

Protection of volunteers after vaccination with Formalin-killed whole piliated organisms has also proved unsuccessful. All of the above vaccines were given parenterally.

POTENTIAL VACCINE CANDIDATES

Pili

Since the human challenge experiments of Kellogg et al. (17, 18), Brinton et al. (4), and Boslego et al. (J. Boslego, J. Ciak, P. Hitchcock, J. Swanson, E. C. Tramont, J. Sadoff, and J. Koomey, unpublished data) indicate a primary role for pili in the pathogenesis of gonorrhea, this review will discuss gonococcal pili in greater detail. Pili are extracellular hairlike structures that either radiate from or encase the gonococcal organisms (43, 47). Pili may allow the organism to attach to epithelial cells or may be antiphagocytic (6, 46, 48, 57). However, data for the latter are controversial (30). Pili are composed of identical pilin subunits with molecular weights of 15,000 to 22,000 (4, 33, 37). Pilins may contain receptor-binding domains (35, 38), although putative pilus-associated proteins may also have functional properties (19, 28, 41). Uropathogenic *Escherichia coli* cells have pili that are composed of pilin and pilus-associated proteins, one of which is the adhesin responsible for the attachment of the organisms to the urogenital tract (21). By analogy, one or more of the gonococcal pilus-associated proteins may also be important in the pathogenesis of gonococcal disease. Thus, the pilus-associated proteins may be future vaccine candidates.

Piliation is a variable state associated with an intact expression site in the gonococcal genome (13, 26, 42, 44). Phase variation from piliation to nonpiliation may involve a deletion event at the expression site (13) or give conversion, resulting in the expression of a missense pilin which cannot assemble (39, 42, 44). In addition, the changes in sequence at the expression site can result in the change of one pilin serotype to another (13, 26, 44). The pilin molecule is about 160 amino acids long. The first 53 amino-terminal amino acids are conserved (39). However, the rest of the molecule is marked by variability (13). Extreme variability occurs between two cysteines at positions 121 and 151 of the molecule. In addition to nucleotide changes which may result in amino acid substitutions, there may be deletions or insertions of enough deoxyribonucleic acid in the genome to delete or add several amino acids. The serological specificity of the response to pilus immunization in laboratory animals appears to be type specific (35, 37, 38). It also appears that in humans, type-specific antibody is protective (4). Because of this extreme variability, pilin immunization may not be feasible. The lack of protection in a field trial with a single pilus vaccine is consistent with this concept.

There do appear to be other, shorter sequences throughout the molecule which are frequently conserved (13, 53). Monoclonal and polyclonal anti-peptide antibodies to several areas in the molecule appear to be cross-reactive (35, 38, 53), and relatively less variability between positions 7 and 92 of the molecule has been most consistently found. This part of the molecule also appears to be immunorecessive in laboratory animals. Peptides made from this amino acid sequence (residues 69 to 84 and 41 to 50) generate cross-reactive anti-pilus antibody that blocks the attachment of gonococci to human cervical cell culture lines (35, 37, 38). It is noteworthy that in the human field trial of the pilus vaccine, cross-reactive antibody arose as a secondary or anamnestic response, indicating the preexistence of anti-pilus antibody. By Western immunoblot analysis, this antibody appeared to be directed to epitopes located in all areas of pilin (unpublished data). Other studies have shown the preexistence of antibody to several outer membrane antigens and have proposed that meningococcal or other bacterial carriage may be responsible for these antibodies (15).

Pilus-associated proteins have been reported by several investigators (19, 28, 41). One study found that there were at least 26 different proteins produced by a piliated organism that were not present in its nonpiliated counterpart (19). Another study found that antibody generated to pili purified by deoxycholate-urea buffer resulted in recognition of not only pili but also five other proteins that were present in piliated organisms but not in nonpiliated organisms (28). Based on binding of both piliated and nonpiliated gonococci to glycolipids, it is postulated that a protein present on both cell phenotypes binds to several glycolipids found in human cervical cell lines (lactosylceramide and gangliotriaosylceramide) (41). The degree of variability of these proteins has not yet been fully ascertained, although they are unlikely to be as variable as the pilin molecule, since they are present in small quantities and may generate little if any immune response in a natural infection. The immunologic pressure for them to vary would therefore be small. Thus, these proteins may be excellent future vaccine candidates.

Protein I

Protein I is the major outer membrane protein of *N. gonorrhoeae*. It is a porin and therefore is responsible for the entry of small molecules through the gonococcal outer membrane (3). Although there is interstrain variation, there is no intrastrain variation. There are two structurally different proteins I, IA and IB, and each has several serotypes (3). Release of protein I into the pericellular area may result in the endocytosis of gonococci by the host cell (3). Antibodies to protein I are bactericidal, and the protein I type may be associated with serum resistance (16, 52, 54). The nature of this association is discussed more completely elsewhere in this issue (31).

Recurrent salpingitis was not associated with isolates processing the same protein I serotype as the isolate from the initial episode of salpingitis (zero of nine patients). On the other hand, cervicitis occurring after an episode of salpingitis was associated with strains possessing the same protein I serotype in 5 of 10 patients. The implication is that the immune response to protein I during salpingitis may result in protein I serotype-specific protection against recurrent gonococcal salpingitis (5).

Protein I is largely embedded in the gonococcal membrane. Some areas are exposed, as determined by enzymatic digests of the outer membrane and genetic experiments involving the construction of hybrid porins (3, 7, 36, 45). Because of the small number of serotypes and the lack of intrastrain variation, protein I has been considered a vaccine candidate. However, a recent study has shown that not all organisms in a population of gonococci may have the protein I epitope(s) exposed on their surface (34). As mentioned above, a human vaccine trial with protein I did not protect against an intraurethral challenge with the homologous strain. This obviously does not rule out the possibility of protection against salpingitis.

Protein II

Protein II is a heat-modifiable protein responsible for the opacity of colonies grown on agar (3). It has been implicated in the adhesion of the organisms to epithelial cells, as well as adhesion between gonococci (3, 20). Progeny of a single gonococcus can produce several protein II types (39). Protein II vaccines would be restricted by the great variability of the antigen.

Protein III

Protein III has been found in all gonococcal strains. It appears not to be variable. Monoclonal antibodies to some epitopes appear to be bactericidal (55). However, recent studies have indicated that IgG present in normal human serum, which blocks bactericidal activity, is directed to protein III (32). Thus, protein III must be viewed with caution as a potential vaccine candidate. Perhaps protein III epitopes (e.g., peptides) that do not raise bactericidal blocking antibodies may prove effective as vaccines.

LOS

LOS, like many of the other antigens of gonococci, has been found to have great variability (12). Anti-LOS antibody is bactericidal (1, 11, 12, 23, 56). LOS may be responsible for the destruction of the host mucosa by acting as a toxin on the mucosal epithelial cells (11). Additionally, LOS determinants share homology with some blood group antigens (23). The homologous determinants may engender tolerance to the common epitopes of LOS or may serve as receptor-binding sites for the gonococci. A vaccine containing LOS

should be considered, but, like many of the other outer membrane antigens, this endeavor will be hindered by the variability of the antigen.

Major Iron-Regulated Protein

The major iron-regulated protein is a 37,000-molecular-weight protein that enables gonococci to utilize iron (25, 27). Following disseminated gonococcal disease, there is an antibody response to the major iron-regulated protein (10). Occasionally, there is a response following uncomplicated local infections (10). Since this protein may be responsible for the survival of the organism in humans, antibody directed to it may be protective. This protein is discussed in more detail elsewhere in this issue (9).

H.8 Antigen

H.8 is a common antigen found in the outer membrane of pathogenic *Neisseria* species. It is unusual in that it is proline and alanine rich and appears to be very hydrophobic (40). Following local infection, antibody to H.8 develops in some individuals (15). Like protein I, H.8 may not be equally exposed on all organisms of a population of gonococci, since electron micrographs show variability in the binding of gold-labeled anti-H.8 antibody (15). H.8 is discussed in more detail elsewhere in this issue (7).

Capsule

A gonococcal capsule associated with resistance to phagocytosis has been described but never isolated (14). Therefore, it is an unlikely vaccine candidate.

IgA Protease

Gonococci elaborate an IgA protease which cleaves IgA immunoglobulin, but its role in infection has not been clearly defined (29).

CONCLUSIONS

Despite much effort and many advances in molecular biology, a vaccine for *N. gonorrheoea* remains an elusive goal. The challenge is made greater by the lack of an animal model and the fact that an effective immune response has never been demonstrated. Piliation is an absolute requirement for urethral infection in men. A pilus vaccine protected men in a challenge study involving the use of a carefully selected clone representing the homologous strain from which the vaccine was made but failed to protect in a field trial. Nevertheless, gonococcal pili or pilus-related proteins remain attractive vaccine candidates. Protein I, protein II, protein III, the major iron-regulated protein, H.8, and LOS are also potential candidates. Indeed, one or more of these cell membrane antigens may be relatively more important in protecting against salpingitis, the complication of gonorrhea that results in the highest morbidity rate. Testing this hypothesis would be very difficult. Finally, it may be time to consider a different strategy, local vaginal immunization. Protecting one-half of the partnership in a sexually transmitted disease will protect the other!

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