Immunity to Group A Streptococcal M Proteins: Forging a Single-Edged Sword

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(See the article by McNeill et al. on pages 1114–22)

Pharyngitis due to group A streptococcus (Streptococcus pyogenes [GAS]) remains one of the most common infections occurring in childhood. Infections due to Streptococcus pyogenes, including skin and soft tissue infections, are believed to account for >10 million cases each year in the United States [1]. Although the number of cases of serious postinfection sequelae—mainly acute rheumatic fever and glomerulonephritis—has decreased markedly in industrialized countries during the past 60 years, these complications remain major causes of morbidity in the developing world, and periodic outbreaks still occur in the United States. The devastating invasive manifestations of GAS disease include necrotizing fasciitis, streptococcal toxic shock syndrome (STSS), bacteremia, and pneumonia. In 2002, the Centers for Disease Control and Prevention estimated that there were 9000 cases of invasive GAS disease and 1200 GAS-associated deaths in the United States.

A pathogen with so diverse an array of disease manifestations would be expected to possess many mechanisms for causing disease, and indeed, numerous virulence factors have been described [2]. Pyrogenic exotoxins account for the syndrome of scarlet fever and play a role in STSS. A hyaluronic acid capsule, present in varying amounts on the surface of virtually all strains of GAS, is essential for both colonization and virulence [3]. Numerous secreted products—including streptolysin, streptokinase, and DNase—are linked to the ability of GAS to cross tissue planes and cause serious disease. However, Rebecca Lancefield, with uncanny insight, recognized the central role of the M protein—found on the surface of GAS—in both virulence and immunity [4]. Lancefield realized that type-specific immunity was imparted by the M protein and that highly virulent isolates produced large quantities of this protein.

M protein is a filamentous molecule that is expressed on the GAS surface as a coiled-coil dimer. The carboxy-terminus, anchored in the cell wall, contains conserved epitopes, whereas the more distal amino terminus displays the characteristic type-specificity. Well over 100 immunologically distinct M proteins are now recognized, with prevalent strains varying over time and geography [5]. In the naive host, the M proteins act to prevent phagocytic cells from killing GAS by binding to plasma proteins that inhibit activation of the complement cascade. Type-specific immunity, developed by contact or infection with GAS with a given M protein, overcomes this deficit and renders the strains susceptible to killing. Individuals with immunity to M proteins are protected from infection with GAS of the same M protein type.

Why, then, have M proteins not been useful vaccines? In an example of “molecular mimicry,” antibodies raised to purified M proteins have been shown in numerous studies to cross-react with cardiac and skeletal muscle myosin, human brain tissues, and molecules of the extracellular matrix (including the glomerular basement membrane) [6, 7]. Immunity to M proteins appears to elicit not just protective immunity, but the potential for autoimmunity as well, and these cross-reactive antibodies have been implicated in the postinfectious sequelae of GAS infection. Indeed, in a trial of a partially purified M3 protein vaccine in 23 healthy children that was conducted in the 1960s, 3 cases of probable or definite rheumatic fever occurred [8]. Although clear causality was never established, the possibility could not be dismissed. Thus, immunity to native M protein, both naturally acquired and vaccine induced, looms as a double-edged sword, providing serotype-specific immunity but also potentially linked to autoimmune sequelae in a small number of individuals.

Although other antigens have been explored for their protective capacity against
GAS infection (for example, carbohydrates and the CSa peptidase), subunit vaccines using M proteins have advanced the farthest. Two approaches have been used to harness the protective immunity of M proteins without incurring the risks of molecular mimicry and autoimmune diseases. One has utilized a conserved, non–cross-reactive C-repeat region of the protein, found in the carboxy-terminal of the protein proximal to the cell wall [9]. Although this approach has the advantage of eliciting immunity to multiple serotypes, and although mucosal immunity has been demonstrated in animal models, these vaccines have not yet advanced to the stage of clinical trials. The second approach is described in this issue of *Clinical Infectious Diseases*. McNeil et al. [10] report the use of a 26-valent vaccine based on the more cell-wall distal, type-specific regions of the M proteins. This group, led by James Dale, has systematically defined the epitopes within each M protein that elicit opsonic and protective antibodies. The vaccine, an impressive feat of bioengineering, is comprised of 4 fusion polypeptides (each with 6 or 7 N-terminal M protein peptides) and systematically excludes epitopes that have been found to evoke tissue cross-reactive antibodies. (An additional antigen—streptococcal protective antigen, or Spa—that appears to elicit protection against several GAS serotypes was included within the vaccine).

In this study, 30 healthy adults were immunized with three 400-µg doses of the 26-valent vaccine along with alum as an adjuvant. As is typical for alum-adjunited protein vaccines, the majority of recipients experienced mild-to-moderate adverse events, such as injection-site reactions, headache, and fatigue. The vaccine elicited significant increases in type-specific antibody in the recipients and the antibodies were opsonic in vitro. For nearly 60% of the M proteins included in the vaccine, geometric mean antibody titer remained significantly elevated 1 year after immunization. More than 80% of the recipients experienced seroconversion (defined somewhat arbitrarily as achievement of an antibody level 2 SDs above that of a panel of normal human serum samples) to 22 of the 26 M types. Importantly, none of the recipients developed tissue–cross-reactive antibodies, as measured by direct immunofluorescence with human tissue samples. The prospect of vaccine-induced protective antibodies to the clinically significant serotypes of GAS, without the attendant risk of autoimmune sequelae, appears for the first time to be within reach.

Major hurdles remain before this or similar vaccines find themselves in clinical use. Large-scale clinical trials involving thousands of participants, including children, will be needed to assess both the safety (because immunologically mediated adverse events may be rare) and efficacy of GAS vaccines. Because in vitro correlates of GAS immunity are poorly defined, carefully chosen clinical end points will be needed. Defining the study population and, similarly, who should be the intended recipients of a GAS vaccine will be difficult. The varying prevalence of M protein serotypes over both time and geography will add difficulty to the design of clinically effective vaccines based on these proteins. A vaccine containing the serotypes prevalent in the United States will likely have less effectiveness in developing countries, where different M proteins predominate. This is unfortunate, because the rates of postinfectious complications, such as rheumatic fever, are far higher in developing countries. Moreover, this type of technology-intensive vaccine is likely to be unaffordable outside of affluent countries. As with other serotype-specific vaccines, the threat of serotype replacement must be carefully considered. The vast number of M proteins, defined both serologically and, more recently, with molecular methods, suggests substantial mutability of the genetic loci encoding the protective epitopes. With high rates of carriage in pediatric populations and the ability of a single virulent strain to spread rapidly through a community, the lifespan of a serotype-specific vaccine might be limited. As with some other vaccines, periodic adjustments to the vaccine composition, as well as strategic periodic reimmunization, may be required to maintain effective coverage.

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**References**


