46

Pneumococcal Common Proteins and Other Vaccine Strategies

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DEVELOPMENT OF NOVEL VACCINES TO PNEUMOCOCCAL ANTIGENS

Streptococcus pneumoniae expresses a number of molecules aside from capsular polysaccharide that are able to elicit protection (Fig. 1). This chapter summarizes data for some of the molecules for which the most complete data have been obtained in animal studies (Table 1). Space constraints prevent description of all potential antigens and all relevant citations.

PHOSPHOCHOLINE/TEICHOIC ACIDS

Phosphocholine (PC) is a common epitope on several respiratory bacterial pathogens (1). PC is an invariant epitope of the teichoic and lipoteichoic acids of all pneumococci, and the demonstrations that mouse and human (2,3) antibodies to PC can protect mice from fatal infection provided the first evidence that a defined antigen other than capsular polysaccharides could elicit protection against pneumococci. However, the PC-epitope on teichoic and lipoteichoic acids does not elicit memory responses; moreover, antibodies to PC are less protective per molecule than those to capsule (4), and isolated PC-containing teichoic acid is not highly immunogenic.

PNEUMOCOCCAL PROTEIN VACCINE ANTIGENS

Protection-eliciting pneumococcal protein(s) provide an attractive alternative to using capsular polysaccharides or polysaccharide-protein conjugates as a vaccine (5). Infants generally make good responses to protein antigens, and the immunogens in successful nonliving pediatric vaccines are generally proteins themselves, or are associated with protein carriers. It should be possible to target several critical virulence and invasion mechanisms by using more than one protein in a vaccine. Immunization with mixtures of pneumococcal proteins can be more protective in mice than immunization with individual proteins (6–8). Since the recombinant proteins are relatively inexpensive to produce, once the substantial costs of performance of clinical trials and the construction of a manufacturing facility have been resolved, a protein vaccine could be affordable worldwide.

The first pneumococcal proteins shown to elicit protection in mice were pneumolysin, PspA, neuraminidase, autolysin, PspC, and PsaA. Each of these proteins was found to play a role in virulence (9). Based on analysis of the pneumococcal genome, the use of in vivo gene selection systems, and identification of antigens recognized by human sera, many additional potential protein vaccine candidates have been identified. Many of these are described below.

PspA

PspA (pneumococcal surface protein A) is expressed by virtually all pneumococci (10) and has been used to immunize human volunteers (11). Human antibodies elicited by immunization with rPspA protect mice from fatal sepsis with pneumococci (12). PspA molecules range in size from about 65 kDa to about 95 kDa (13). The N-terminal α-helical half of the molecule has an antiparallel coiled coil structure (14), is surface exposed (15), and is protection eliciting (12). The center of the molecule contains about 80 residues, 40% of which are proline. Over half of PspA molecules have a 33-residue highly conserved nonproline-containing region in the center of the proline-rich region. The proline-rich region and its nonproline block are surface-exposed and protection eliciting. The C-terminal end of the molecule contains conserved choline-binding repeats that attach PspA to the PC residues of the cell surface lipoteichoic acids.

Although PspA exhibits structural variability (13), protective antibodies elicited to the N-terminal coiled coil domain and proline-rich region are quite cross-reactive (12,16). Ninety-eight percent of PspAs exist in two cross-protective PspA families (10,13,17). Antibodies elicited to PspA in mice, rabbits, and humans can protect mice from intravenous infection with pneumococcal challenge strains (9). It is expected that a PspA vaccine will not need more than three PspAs (12,18).