Meningococcal Vaccines and Mucosal Immunity

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Neisseria meningitidis causes a devastating invasive disease but is also a normal colonizer of the human nasopharynx. Due to the rapid progression of disease, the best tool to protect individuals against meningococcal infections is immunization. Clinical experience with polysaccharide conjugate vaccines has revealed that an ideal meningococcal vaccine must prevent both invasive disease and nasal colonization, which confers herd immunity. However, not all meningococcal vaccines are equal in their ability to prevent nasal colonization, for unknown reasons.

Keywords: meningococcus ; nasal infection ; sepsis ; vaccine ; mucosal immunity ; herd immunity ; 4CMenB ; humanized mouse model

1. Introduction

Neisseria meningitidis (the meningococcus) is a Gram-negative bacterial pathogen that is an obligate colonizer of the human nasopharynx. Nasal colonization is asymptomatic in nature; however, under rare circumstances, *N. meningitidis* can penetrate mucosal tissues to cause severe invasive disease [1]. Invasive meningococcal disease most commonly presents as meningitis and sepsis, but may also cause gastrointestinal symptoms, septic arthritis, pericarditis, and invasive pneumoniae [2][3]. If left untreated, invasive meningococcal disease is lethal in upward of 50% of patients [4]. Despite the availability of effective antibiotic treatment options, fatality rates remain above 10%, with a large percentage of survivors experiencing serious lifelong morbidities [5][6]. The most effective way to reduce the burden of invasive meningococcal disease is through immunization, and much effort has been devoted toward the development of meningococcal vaccines.

The most successful meningococcal vaccines currently in use are those that use capsule polysaccharides conjugated to a protein carrier as the vaccine antigen [4]. *N. meningitidis* serogroups are defined on the basis of capsule polysaccharides to give a total of 13 serogroups, of which six (A, B, C, W, X, and Y) are responsible for the vast majority of invasive meningococcal disease [4]. Vaccines using capsule polysaccharides are available for serogroups A, C, W, and Y. Polysaccharide conjugate vaccines are extremely successful at preventing invasive disease by the respective serogroups in vaccinated individuals, and they have the added effect of preventing *N. meningitidis* nasal colonization; this has been particularly evident following immunization with capsule-conjugate vaccines targeting serogroup C and serogroup A [7][8][9][10][11][12][13][14]. Prevention of nasal colonization reduces the transmission of vaccine serogroups through a vaccinated population, thus reducing the risk of invasive disease in unvaccinated or otherwise nonimmune individuals. This immunity to nasal colonization is exemplified in the reduced nasal burden observed during carriage studies, as well as reduced invasive disease documented in unvaccinated individuals. The indirect protection against invasive disease afforded to unvaccinated individuals is referred to as herd immunity [15][16].

Following the success of conjugate vaccines in controlling meningococcal disease through the induction of herd immunity, prevention of nasal colonization is now considered the gold standard to which all future meningococcal vaccines strive [15]. Unfortunately, the immune processes that confer protection against meningococcal nasal colonization are poorly understood, making it difficult to target these processes during vaccine design. This challenge is exacerbated because *N. meningitidis* does not naturally colonize the nose of any organism other than humans, which hampers understanding of processes related to nasal colonization, as well as preclinical evaluation of vaccines. Without an animal model or an accepted correlate of protection against nasal colonization, meningococcal vaccines have been approved without any predicted effect on mucosal immunity. Impact on nasal colonization is, therefore, only appreciated after vaccine implementation, through large clinical studies and immunization campaigns.

2. CEACAM1-Humanized Mice as a Model for Meningococcal Nasal Colonization

Wild-type mice are not colonized by *N. meningitidis*. The introduction of a transgene encoding the human carcinoembryonic antigen-related cell adhesion molecule 1 (hCEACAM1) renders mice susceptible to nasal colonization by *N. meningitidis* [17][18][19]. These transgenic mice, herein referred to as hCEACAM1 mice, present a useful tool to shed light onto the meningococcal lifestyle within the mucosa and host–pathogen interactions that occur during meningococcal nasal infection.

While mice express CEACAM1, *Neisseria* do not bind the murine ortholog. Expression of the hCEACAM1 transgene mirrors the pattern seen in human tissues and, importantly, is expressed in the nasopharynx where it can be accessed by *N. meningitidis* during nasal infection [17][19]. Colonization is quantified by the number of colony-forming units (CFU) recovered from the mouse nose at various time points following infection [17]. A diverse array of meningococcal strains are capable of colonizing hCEACAM1 mice, including historically relevant lab strains [17][20], as well as low-passage clinical strains [21]. *N. meningitidis* binds to hCEACAM1 via its colony opacity-associated (Opa) proteins [17]. Colonization of hCEACAM1 mice is strictly dependent on the interaction between neisserial Opa proteins and mouse hCEACAM1 expression. Opa expression is controlled by phase variation in N. meningitidis and is, therefore, turned randomly ‘on’ and ‘off’ during bacterial growth and division. Bacteria that are genetically *opa*-deficient fail to colonize hCEACAM1 expressing mice [17]. Furthermore, when an inoculum was prepared with only phase variants that had Opa expression turned ‘off’, all bacteria recovered from mice were expressing Opa proteins, thus reflecting an in vivo selection for Opa expression [17]. This finding parallels studies done in human volunteers with *Neisseria gonorrhoeae*, wherein an inoculum was prepared with Opa expression turned ‘off’, but all bacteria recovered from the urethra of male volunteers were Opa-expressing [22]. Thus, the importance of the interaction between Opa and hCEACAM1 demonstrated in the mouse model is reflective of an important interaction during human infection.

Colonization of hCEACAM1 mice is variable for different strains in terms of rate of colonization (number of mice colonized) and burden of colonization (CFU recovered per mouse). Some strains tested will colonize upward of 90% of infected mice, while others will colonize as few as 20–30% of mice ([17][20][21] and unpublished data). Colonization is also short-term, with most transgenic mice clearing nasal infection within 10–14 days post inoculation, corresponding with the time required for the emergence of an adaptive immune response [17]. In humans, colonization can be chronic and last up to a year [23]. This short-term colonization in mice is likely reflective of the extreme human restricted nature of *N. meningitidis*, given that the meningococcus binds only the human forms of various host proteins, including those for iron acquisition and complement evasion. The addition of other human factors may increase utility of this model in studying chronic infections. However, in its current form, the hCEACAM1 model still presents an opportunity to study many factors surrounding meningococcal colonization in a living organism, including the innate and adaptive immune responses to infection, as well as testing the efficacy of drugs, immunotherapies, and vaccines.

3. Polysaccharide Conjugate Vaccines

Polysaccharide conjugate vaccines are capable of inducing protection against meningococcal nasal colonization in humans [7][8][9][10][11][12][13][14]. Plain polysaccharides are T-cell-independent antigens that are poorly immunogenic in children and do not induce long-lasting immunity in adults [24]. The covalent linkage of polysaccharides to a protein carrier converts polysaccharides into T-cell-dependent antigens, which results in increased antibody titers post vaccination that are sustained for longer periods of time, most likely due to T helper cells facilitating B-cell maturation [25][26]. However, for historical reasons, the protein carriers used in currently licensed meningococcal conjugate vaccines include either the chemically inactivated tetanus or diphtheria toxoids, or an inactivate mutant of the diphtheria toxin, CRM197, none of which are expressed by *N. meningitidis* [4]. The protection afforded by these conjugate vaccines will, therefore, be restricted to B cell, plasma cell, and antibody responses to the capsular polysaccharide, since the protein-specific responses are irrelevant to the meningococci. However, parenteral immunization does not elicit mucosal IgA, which is classically attributed to mucosal protection. Given that little is known regarding the effector mechanisms of systemically produced IgG within the nasal mucosa, the relative contribution of complement, opsonophagocytic, or other processes to protection against meningococcal colonization remains unknown.

Vaccine-elicited antibodies that induce complement-dependent killing, as measured by serum bactericidal assay (SBA), are instrumental in protection against invasive meningococcal infections and are currently used as a correlate of protection during vaccine development [15]. While polysaccharide conjugate vaccines induce robust SBA titers in serum [27], antibody opsonization leading to phagocytic killing of the meningococcus has also been reported as an important mechanism of clearance of *N. meningitidis* infections [28][29]. Moreover, protection against colonization by other bacterial

pathogens has been attributed to antibody-dependent bacterial agglutination [30][31]. The mechanism through which polysaccharide conjugate vaccine induced meningococcal specific antibodies facilitate clearance of nasal colonization is currently unknown. Notable in this regard, immunization of hCEACAM1 mice with the serogroup C capsule-conjugate vaccine protected against nasal colonization [17], recapitulating the protection observed in humans. This provides an opportunity to evaluate how anti-capsular antibodies confer immunity against nasal colonization in these mice, and to test whether these processes could be promoted through different vaccination formulations and/or routes of administration.

4. Protein Vaccines

The majority of invasive meningococcal infections in Europe and North America are caused by serogroup B *N. meningitidis* [32]. While polysaccharide-based vaccines have effectively targeted select serogroups of *N. meningitidis*, the serogroup B capsule polysaccharides mimic human antigens and are, therefore, unsuitable for use as a vaccine component [33]. Two vaccines, 4CMenB and rLP2086, are currently approved for the prevention of serogroup B *N. meningitidis* [34][35][36]. This review focuses on the impact of 4CMenB immunization since these have been tested against meningococcal colonization in the CEACAM1-humanized mice.

A difficulty with interpreting the impact of 4CMenB immunization on nasal colonization is that this vaccine is a subcapsular vaccine. Unlike experience with capsule polysaccharide vaccines, implementation of 4CMenB is not expected to completely abrogate invasive disease caused by serogroup B strains because the targeted antigens vary in sequence and expression level [37]. Further, while 4CMenB was developed with specific focus on serogroup B meningococcal strains, immunization can also impact strains that are not serogroup B due to shared antigens [37]. This means that monitoring total serogroup B nasal colonization rates may not capture the total impact of 4CMenB immunization.

Immunization with 4CMenB elicits robust protection against invasive disease in mice however, in contrast, immunization did not confer protection against nasal colonization by approximately half of the strains tested in hCEACAM1 mice [21]. This suggests that antibody responses, while being reliable predictions of protection against invasive disease, do not predict protection against colonization. This finding is in agreement with clinical studies, where immunized individuals are protected against invasive disease, but no observable impact on colonization or herd immunity has been documented [38][39][40][41].

It is instructive that 4CMenB immunization did confer protection against colonization by some of the challenge isolates. Immunization prevented colonization by strain NZ98/254, which matches vaccine antigens PorA and fHbp and is the source of the vaccine's OMV preparation, and by two out of the three tested low-passage clinical isolates, which matched vaccine antigens PorA, NHBA, and fHbp or PorA and fHbp, respectively [21]. Prevention of colonization by strains that express numerous vaccine antigen matches may suggest that mucosal immunity elicited by 4CMenB requires a high density of targeted epitopes on the bacterial surface, either due to high-level expression or reactivity against multiple antigens. Experimental validation of this point may allow the potential impact of this and other protein-based vaccines on community carriage to be more effectively modeled.

5. Outstanding Questions and Future Directions

While the invasive phases of disease cause the devastating consequences of meningococcal infection, these necessarily follow nasopharyngeal colonization. Thus, effective mucosal immunity will protect the immune individual while also providing herd protection. Despite its importance, the lifestyle of meningococci within mucosal tissues remains poorly understood, and the determinants of sterilizing immunity remain undefined. Exemplifying this point, a number of factors have been associated with increasing an individual's risk of *N. meningitidis* nasal carriage have been defined which include smoking in British teenagers [42], the dry season in the meningitis belt in Africa [43][44], and previous influenza infection [45], however a mechanistic explanation for these associations remains unknown. While mouse models cannot replicate all aspects of infection, judicious development and application of new models can allow direct questions such as these to be addressed. Similarly, mechanistic studies comparing the relative efficacy of different immunization strategies can shed light onto what immune processes confer mucosal protection, and how to improve cross-protection so as to provide broad-spectrum coverage against all meningococcal strains. Mouse-based studies with other human upper respiratory tract pathogens, including *Streptococcus pneumoniae* [46][47][48][49] and *Bordetella pertussis* [50][51][52][53], highlight the utility of this approach by revealing an unexpected contribution of T lymphocytes as the effectors governing nasal protection. Thus, by combining bacterial and mouse genetics with drug and immune-based interventions, the humanized mouse models can test hypotheses and provide new insight regarding the specific contribution of putative

virulence factors to infection and disease, to understand the fine balance between immunity and immunopathogenesis, and to reveal where rational vaccine design may further enhance protection.

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