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Animal Models for Pathogenic *Neisseria* Species

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The development and use of various animal models in the early 1970s helped renew interest in the immunobiology of *Neisseria gonorrhoeae* and *N. meningitidis*. This research also provoked controversy concerning which infection model provided the most useful information. Certainly, the human host or isolated organ cultures provided a relevant test system for neisserial infections; however, these models were not accessible to many research groups, and, therefore, alternative models were necessary for preliminary studies. If some discretion is exercised in selecting an appropriate species and in interpreting the results, much useful information can be obtained by studying these sometimes contrived model systems. The question regarding what constitutes a valid model depends largely on the types of experiments being performed. For cell attachment studies, human tissues appear to be essential because of the species-specific nature of this interaction (27). Human organ cultures that may be ideal for studying receptor-mediated attachment may be less suitable for studying the role of humoral factors in pathogenesis because some cell- and complement-mediated systems are not intact. On the other hand, certain animals whose immune systems function in many respects like those of humans can be used to study the complex interaction of the multiple cellular and humoral factors that are involved in the inflammatory response, even though these animals may lack the species-dependent receptors found in tissues of human origin. In this article I will review some of the attributes and deficiencies inherent in the various animal species that have been used as models of infection and point out the aspects of their comparative immunology that are important in interpreting results.

ANIMAL MODELS OF *N. GONORRHOEAE* INFECTION

Some of the earliest published reports of animal infections involving *N. gonorrhoeae* appeared in the late 1930s when Miller described the mouse intraperitoneal and rabbit intraocular models (35, 36). The rabbit model was used briefly for testing the in vivo efficacy of new antimicrobial agents, but the overwhelming success of penicillin in human trials soon thwarted interest in continued animal testing. The next flurry of activity in this area occurred in the early 1970s, when studies of genital infections of chimpanzees (5, 12, 31) and infections of subcutaneous chambers in laboratory animals (1–3, 6, 16) were reported. Results from immunologic studies involving these models heightened interest in the use of animals and in the prospect of developing a successful gonococcal vaccine.

Primate Infection

The chimpanzee (*Pan troglodytes*) is the only animal species other than humans in which localized urethral infections of 3 to 6 weeks in duration have been established (31). Anatomically and physiologically, chimpanzees resemble humans; they have similar ABO blood groups, serum lysozymes, and an immunoglobulin A susceptible to cleavage by gonococcal immunoglobulin A protease (40). Chimpanzees have been infected with laboratory-grown gonococci, and male-to-female transmission has occurred in sexually active cage mates (12). Not unlike the situation in humans, individual variation in susceptibility to gonococcal infection has been observed. Chimpanzees that have urethras colonized by *Proteus* and *Serratia* spp. can show greatly increased resistance to gonococcal infection. In addition, not all human isolates of gonococci are virulent for chimpanzees (4, 30). Nevertheless, chimpanzees have been useful for demonstrating relative, strain-dependent, acquired resistance to *N. gonorrhoeae* following experimental infection or systemic immunization with formaldehyde-fixed cells (4, 5). Interestingly, a greater degree (≥200-fold) of resistance to urethral infection was induced by systemic immunization with formaldehyde-fixed cells than was observed following remission of untreated urethral infection (4, 5, 30). In addition to the enhanced resistance to urethral challenge, immunized male chimpanzees became colonized with relatively fewer gonococci when given an overwhelming challenge dose ($>10^7$ colony forming units), remained infected for a shorter period, and were unable to infect susceptible females (4, 5). Unfortunately, male chimpanzees suitable for gonococcal studies are in limited supply, and their use as a model for human immunodeficiency virus infection will further diminish prospects of their use in other types of research.

Nonprimate Infection

Except for some differences in their comparative immunology, laboratory animal species are readily available for certain types of infection-related experiments. A number of inbred lines of immunologically well-characterized mice are available, and gonococcal infections can be induced in this species by a variety of methods. Mice implanted with subcutaneous chambers are well adapted for graded-dose challenge experiments, which permit the determination of relatively small differences in the virulence of *N. gonorrhoeae* strains or in the acquired resistance of the host. Because some strains of mice are deficient in complement factors necessary for efficient bactericidal activity via the classical pathway, a method has been developed for administering exogenous guinea pig complement at the time of gonococcal challenge. This technique allows some aspects of both complement-dependent and complement-independent resistance to be quantitatively determined (8, 24, 49).

At least two methods for inducing urogenital infections in mice have been reported: inoculation of gonococci into fluid-filled perianal sacs formed by natural or surgically produced strictures of the uterus (11, 51), and transcervical inoculation of gonococci (29). Both methods produce histologic evidence of inflammation, and viable gonococci can be recovered from infected tissues at various days after inoculation. These models offer the advantage that gonococcal infections are induced in a more natural site. However, because murine immunoglobulin A is not susceptible to gonococcal proteases and because the gonococci remain

entrapped in a fluid-filled cavity, these models may not prove suitable for some experiments that examine mucous-membrane attachment, especially when host-specific surface receptors are involved.

Because of their relatively high level of serum complement activity, guinea pigs are often preferred as immunologic models. However, the only reported method for inducing gonococcal infections in this species involves implanted porous chambers (2, 9). The foreign-body effect produced by the subcutaneous chamber appears to create an immunologically privileged site where gonococci can be grown for several weeks before the host immune system terminates the infection. Because small-challenge inocula (10 to 100 colony-forming units) of several gonococcal strains can produce high (>80%) infection rates, guinea pigs are a sensitive model for determining some aspects of acquired resistance induced by systemic immunization (6, 7). By using a graded-dose challenge method, a significant level of strain-related and cross-protective immunity can be quantitatively determined (7, 38, 52). Most strains of gonococci recovered from urogenital infections can infect guinea pigs. Paradoxically, some strains, especially those of the IA-2 serovar often found associated with disseminated gonococcal infections, are not as virulent for guinea pigs (37). This difference may be due to species-related differences in protective host factors such as the availability of metabolic iron, immunoglobulin classes, blocking antibodies, or in S protein, an important inhibitor of terminal complement factors (32, 41).

Rabbits are convenient animals for the production of immune sera, but they are not highly susceptible to subcutaneous neisserial infections unless they are given large doses of dexamethasone, an immunosuppressive drug that inhibits synthesis of interferon by decreasing the level of its messenger ribonucleic acid (23). However, by using a transaortic catheter, one can produce a gonococcal bacteremia in rabbits that results in hepatic lesions similar to those observed in humans (28). Rabbits are generally sensitive to the effects of bacterial endotoxin, and a generalized Shwartzman reaction can be induced by giving two intravenous injections of gonococci 20 to 24 h apart (10). However, attempts to use a rabbit oviduct organ model for studying gonococcal cell attachment have been unsuccessful because only human tissue provides for specific attachment and mucosal damage. Oviducts of bovine and porcine origin were likewise undamaged by gonococci (27).

Laboratory rats are not easily infected with gonococci, probably because of their high level of natural serum bactericidal activity. Rats have been used, however, to demonstrate the arthropathic properties of the gonococcal peptidoglycan that has been implicated in the pathogenesis of disseminated joint disease (20).

Gonococcal infections produced in subcutaneous chambers implanted in hamsters are similar to those described for laboratory mice. Hamsters have a better-developed complement system than do most strains of mice, but their very short tail makes them difficult to handle and increases the risk of the handler's being bitten.

Chicken embryos provide a convenient model for in vivo studies involving some aspects of neisserial pathogenesis (14, 15, 21, 47). However, they lack a complete complement system and are not amenable to active immunization, although the effects of passively transferred antibodies have been tested in this model (19).

ANIMAL MODELS OF MENINGOCOCCAL INFECTION

Various animal models including monkeys, rabbits, guinea pigs, mice, and chicken embryos have been used in the study of different aspects of meningococcal pathogenesis (18, 22, 34, 44). Of these species, the laboratory mouse is probably one of the more versatile animals in terms of methods for inducing infection, because we can select inbred lines with well-characterized immunologic features. The influence of genetic loci on the susceptibility of mice to bacterial invasion is well documented (43). The *Lps* gene locus, which regulates the cellular response to endotoxin, appears to have significant control over the host resistance to meningococcal infection (42, 53). Inbred lines of mice with a defective *Lps* response fail to appropriately activate macrophages during the early stages of infection, resulting in microbial colonization and subsequent hematologic dissemination. However, one must also appreciate that although *Lps*-defective mice can support more rampant bacterial growth, their immunologic and pathologic responses to infection could also be severely compromised.

The mouse intraperitoneal infection model that uses gastric mucin to enhance infection has been used extensively for determining meningococcal strain variation and for elucidating the role of metabolic iron during meningococcal infection (34). Because very little free iron is available to microorganisms growing extracellularly in the human or animal host, many pathogens have developed methods for obtaining essential iron from storage and transport proteins. Both meningococci and gonococci are capable of obtaining iron from transferrin and lactoferrin, whereas most commensal *Neisseria* organisms lack this capacity (33). Holbein found that iron dextran could replace mucin in the mouse intraperitoneal model and suggested that an iron deficiency developed in mice following infection as a result of the failure of transferrin to reload iron (25). Holbein later showed that some virulent strains of meningococci could infect mice independent of exogenous iron, and he suggested that virulence determinants, in addition to iron acquisition, played an important role in pathogenicity (26). Both Miller (34) and Holbein (25) proposed that carrier strains of meningococci may lack the invasiveness of disease strains; therefore, research continued toward developing a relevant infection model that could determine the invasive potential of test organisms.

The mouse intraperitoneal model was shown to have some capability for discriminating between meningococci of high and low virulence. Disease-associated strains generally induced a fatal infection in mice after the injection of relatively few microorganisms (<10 colony-forming units), whereas less virulent or carrier strains had a 50% lethal dose of $>10^4$ colony-forming units (26). Salit (44) described a mouse model in which intranasal challenge was used to test the invasive potential of disease- and carrier-associated strains. Approximately 40% of 2- to 5-day-old mice became bacteremic by 48 to 72 h after intranasal inoculation with virulent meningococci. This model offered an advantage in that meningococcal attachment, mucosal colonization, and invasion of underlying tissue with subsequent hematologic dissemination could be monitored in systematic experiments involving histologic sectioning of the intact mouse.

An infant-rat model for group B meningococci has been developed to evaluate the protective effects of monoclonal antibodies that react with class 1 and class 3 outer membrane proteins (45, 46). Five-day-old Wistar rats were injected intraperitoneally with monoclonal antibodies 1 or 20 h before

the intraperitoneal injection of 10^5 colony-forming units of a group B meningococcal strain. These monoclonal antibodies gave significant protection against the subsequent bacteremia, meningitis, and death that occurred in the control animals. Peppler and Frasch previously showed that guinea pigs could be protected against group B meningococci by immunization with a serotype 2 vaccine (39). These models are convenient tools for evaluating the systemic effects of various immunologic interventions. Additional factors that are important in the human disease, however, such as the effects of immunologic maturity of the host, the role of mucosal attachment, and tissue invasion, must also be considered if an appropriate model is to be developed.

ORGAN CULTURE MODELS

The human fallopian tube organ culture has provided researchers with an excellent system in which to study the gonococcus-host cell attachment and the localized spread of microorganisms. In this model, the initial attachment of gonococci to nonciliated host cells appeared to be mediated by the interaction of gonococcal pili with microvilli of the mucosal cells (27, 48). The release of cytotoxins, including lipopolysaccharide and monomeric peptidoglycan, resulted in injury to the host cells as evidenced by the loss of ciliary activity and eventual sloughing of the cells. Important questions concerning tissue penetration by gonococci and the effects of immunoglobulin A protease have been addressed by using organ culture (17). Endocytosis and phagocytosis of gonococci by host cells appear to play major roles in the translocation of gonococci to the subepithelial space in organs where the bacteria can multiply.

Another organ culture, containing human nasopharyngeal tissue, has been used to evaluate the interaction of *N. meningitidis* with mucous membranes. Meningococci selectively attached to the microvilli of nonciliated epithelial cells and were internalized by endocytosis. Although meningococci failed to attach to ciliated cells, ciliary function and cell viability were damaged by lipopolysaccharide released by the microorganisms (48).

CONCLUSIONS

Although many successful experiments have been reported, the use of various animal models to test the virulence and immunogenicity of *Neisseria* spp. remains controversial. Animal trials with chimpanzees, guinea pigs, and mice have shown that significant immunity, either relative or absolute, can be induced by systemic immunization with formaldehyde-fixed cells or with protein outer membrane complex. No increased resistance was obtained, however, by administering preparations of highly purified gonococcal pili (13, 50). The relative degree of cross-protection afforded by immunization with different neisserial strains has also been shown in these models. Surprisingly, results of gonococcal immunization trials in these species appear to be consistent, even though the routes of infection, intraurethral for chimpanzees and subcutaneous in mice and guinea pigs, are very different. The ability to test various immunogens in animal models has allowed researchers to establish that systemic immunization can affect strain-related resistance to *Neisseria* spp. and should continue to provide an alternative method for preliminary testing of potential vaccines.

Many unanswered questions exist concerning the attachment and in vivo growth of pathogenic *Neisseria* spp. The role of pili is not completely understood. The nature of the receptors that mediate specific attachment of cells and lipopolysaccharides also awaits further definition. The species-specific binding of *N. gonorrhoeae* and *N. meningitidis* with host proteins, including transferrin, lactoferrin, and S protein, is being studied in an attempt to isolate cell components that could have vaccine potential. The preliminary testing of these candidate vaccines will probably involve animal studies. Therefore, it is essential that investigators select the most appropriate model, based on current information concerning the pathogenic mechanism of infection and the type of vaccine intervention being tested.

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