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Inhibition of *Borrelia burgdorferi*-Tick Interactions In Vivo by Outer Surface Protein A Antibody

Utpal Pal,* Ruth R. Montgomery,* Denise Lusitani,† Pierre Voet,‡ Vincent Weynants,† Stephen E. Malawista,* Yves Lobet,† and Erol Fikrig*‡

*Borrelia burgdorferi* outer surface protein (Osp) A is preferentially expressed by spirochetes in the *Ixodes scapularis* gut and facilitates pathogen-vector adherence in vitro. Here we examined *B. burgdorferi*-tick interactions in vivo by using Abs directed against OspA from each of the three major *B. burgdorferi* sensu lato genospecies: *B. burgdorferi* sensu stricto, *Borrelia afzelii*, and *Borrelia garinii*. Abs directed against *B. burgdorferi* sensu stricto (isolate N40) destroy the spirochete and can protect mice from infection. In contrast, antisera raised against OspA from *B. afzelii* (isolate ACA-1) and *B. garinii* (isolate ZQ-1) bind to *B. burgdorferi* N40 but are not borreliacidal against the N40 isolate. Our present studies assess whether these selected OspA Abs interfere with *B. burgdorferi*-tick attachment in a murine model of Lyme disease with *I. scapularis*. We examined engorged ticks that had fed on *B. burgdorferi* N40-infected *scid* mice previously treated with OspA (N40, ACA-1, ZQ-1, or mAb C3.78) or control Abs. OspA-N40 antiserum or mAb C3.78 destroyed *B. burgdorferi* N40 within the engorged ticks. In contrast, treatment of mice with OspA-ACA-1 and OspA-ZQ-1 antisera did not kill *B. burgdorferi* N40 within the ticks but did effectively interfere with *B. burgdorferi*-*I. scapularis* adherence, thereby preventing efficient colonization of the vector. These studies show that nonborreliacidal OspA Abs can inhibit *B. burgdorferi* attachment to the tick gut, highlighting the importance of OspA in spirochete-arthropod interactions in vivo. *The Journal of Immunology*, 2001, 166: 7398–7403.
burdorferi-infected mice has little or no effect on the murine infection, but such Abs are able to interfere with the establishment of B. burgdorferi infection within the feeding tick (17, 20). The temporal and tissue-specific expression of OspA in the gut of the tick suggests that OspA may have a function in the vector, and we have recently shown that OspA mediates the attachment of B. burgdorferi to I. scapularis in vitro (21). In our study, recombinant nonlipidated OspA from B. burgdorferi bound to the I. scapularis gut tissue and this attachment was partially abrogated by site-directed mutagenesis of OspA aa 229–247 (21).

Here we examine spirochete-tick adherence in vivo by using the differential protective capacity of OspA antisera from selected Borrelia genospecies. It has been shown that antigenic diversity in OspA among the B. burgdorferi sensu lato genospecies can result in a lack of cross-protection by OspA antisera (22, 23). For instance, OspA antisera against a B. burgdorferi sensu stricto isolate may not necessarily protect mice against challenge with a B. afzelii or B. garinii isolate and vice versa (22, 23). Protective OspA Abs prominently bind to epitopes within the carboxyl terminal half of OspA, and antigenic diversity within this region of OspA influences the ability of protective OspA Abs to kill B. burgdorferi (24, 25). For example, active immunization of mice with OspA from B. burgdorferi N40 or passive immunization with OspA-N40 mAb C3.78 is protective against B. burgdorferi N40 but not B. burgdorferi 25015 (26). This lack of cross protection is attributable to several amino acid differences in the carboxyl terminus of OspA between B. burgdorferi 25015 and B. burgdorferi N40 that alter the ability of protective B. burgdorferi OspA N40 Abs to bind to B. burgdorferi 25015 (26). Therefore, we now have used OspA mAb C3.78 and OspA antisera from three B. burgdorferi sensu lato genospecies, B. burgdorferi sensu stricto (isolate N40), B. afzelii (isolate ACA-1), and B. garinii (isolate ZZ-1), to differentiate the roles of in vitro characterized borrelioidal and nonborrelioidal OspA Abs in spirochete-vector interactions and to investigate the importance of OspA in B. burgdorferi-tick adherence in vivo.

Materials and Methods

B. burgdorferi and I. scapularis

A low-passage clonal isolate of B. burgdorferi N40 that is infectious to mice was used throughout (27). Spirochetes were cultivated in Barbour-Stoenner-Kelly (BSK) II medium at 33°C. Adult female I. scapularis ticks were collected in Connecticut. The egg mass was laid in the laboratory. Hatched larvae were allowed to feed on uninoculated C3H mice to produce pathogen-free nymphs. All tick rearing was performed in an incubator at 37°C for 1 h. After incubation, with tetramethylbenzidine peroxidase substrate (Kirkegaard & Perry Laboratories, Gaithersburg, MD) for 15 min, the absorbance at 450 nm was measured.

Immunoblot

Wild-type or mutant recombinant OspA Abs from B. burgdorferi N40 with selected amino acid mutations (designated M4, M5, and M6) in the major tick gut-OspA binding epitope (aa 229–247) were expressed and purified if the lipidated form of the recombinant OspA was lipidated. Abs were probed with OspA mAb C3.78 by immunoblot. Two micrograms of recombinant OspA were electrophoresed in a 10% SDS-PAGE, transferred onto nitrocellulose membranes, and then incubated with mAb C3.78 (1/100 dilution). The signal was detected with a goat anti-mouse IgG-conjugated alkaline phosphatase (Sigma).

Ab characterization in vitro

Immunofluorescence. For staining of cultured spirochetes, B. burgdorferi N40 (10^5 spirochetes/ml) were suspended in PBS and 10μl aliquots were placed on sialylated glass slides (PGC Scientific, Gaithersburg, MD) and allowed to air dry. Each slide then was fixed with acetone for 5 min at 37°C. The slides were washed three times with PBS, and incubated in PBS-T with 5% FCS (blocking buffer) for 30 min at room temperature. The slides were then labeled with OspA antisera at a dilution of 1/100 in blocking buffer, washed, and subsequently incubated for 1 h with FITC-labeled goat anti-mouse IgG (Sigma). The samples were washed three times with PBS-T, mounted in glycerol, and examined with a Zeiss Axioskop fluorescence microscope (Carl Zeiss, Thornwood, NY).

[3H]Adenine incorporation and bactericidal assay. Asbs were tested for their bactericidal activity against B. burgdorferi N40 both by dark-field microscopy and by monitoring the uptake of [3H]adenine (31, 32). Spirochetes (5 x 10^6/ml) were incubated in rabbit sera (Sigma) with selected OspA or control Abs (1/25 dilution) for 24 h at 37°C, after which the percentage of viable spirochetes was determined by dark-field microscopy. Following 1-ml aliquots of aliquots were placed in 96-well plates with 200 μl of BSK/20% rabbit serum/[3H]adenine (5 μCi/well; ICN Biomedical), for 48 h at 33°C. Incorporation of [3H]adenine by dividing spirochetes increases in a linear fashion over 48 h with a spirochete density of 1 x 10^6 to 1 x 10^7/ml (31). In addition, for visual detection of spirochete motility, aliquots (10 μl) were assessed for spirochete motility and refractivity in five random fields by dark-field microscopy. Spirochetes were considered killed when complete loss of motility and refractivity was observed. Control samples were treated with PBS or control nonbacterial B. burgdorferi N40 Abs such as OspF or ErpT antisera. In addition, 100-μl samples were removed from each tube, inoculated into 5 ml of BSK medium, and incubated at 33°C for 5 days. The B. burgdorferi then were counted, and these results were compared with the initial viability by dark-field microscopy in a doublers maneuver. Bacterial viability also were performed with different concentrations of OspA mAb C3.78.

In vivo infection and adherence studies

Pathogen-free NC-1 immunodeficient mice (NCI-SCID) from the National Institutes of Health (Bethesda, MD) were infected with B. burgdorferi N40 (10^5 spirochetes/mouse, 3–5 animals/group) by intradermal injection into the back. After 4 wk, mAb C3.78 (2.5 μg) or selected polyclonal antisera were administered to groups of mice (100 μl i.p. and 100 μl s.c.). Twenty-five days later, 10 I. scapularis nymphs were placed on each mouse. The animals again were treated with mAb or antisera on the next day. The nymphs were allowed to feed to repletion and detach from the mice, which usually occurred at ~72 h. Guts from each group of nymphs were dissected under a microscope in PBS (20 μl/gut) and examined at 24, 48, 72, and 96 h after tick detachment. Five-microliter aliquots were examined for anti-OspA antibacterial Abs by dark-field microscopy. Selected nymphs from each group also were reared in an incubator at 26°C with 85% relative humidity and a 12-h light-dark photoperiod regimen for ~1 mo until they molted to adults.

ELISA

Microtiter wells (ICN Biomedical, Costa Mesa, CA) were coated with 0.1 μg of recombinant OspA-N40 and incubated overnight at 4°C. Nonspecific sites then were blocked by PBS with 15% FBS. The wells were incubated with 100 μl of OspA antisera in PBS with 0.05% Tween 20 (PBS-T) at 37°C for 1 h. Abs specific for OspAs were detected with HRP-labeled goat anti-rabbit IgG (Sigma, St. Louis, MO) for 1 h at 37°C. After incubation, with tetramethylbenzidine peroxidase substrate (Kirkegaard & Perry Laboratories, Gaithersburg, MD) for 15 min, the absorbance at 450 nm was measured.
Organs from nymphal ticks were prepared for microscopy as described previously (33) by dissection of gut diverticula in PBS (20 µg/gut). The lumens of each gut diverticulum was exposed by a vertical incision with a fine blade so that individual diverticula were separated from each other, and both ends were opened to facilitate outflow of blood. The organs were washed three times under a dissecting microscope until the cessation of visible flow of blood from open diverticula. The isolated organs were placed on sialized glass slides (PGC Scientific) to enhance attachment, allowed to dry, and fixed with acetone for 5 min. Acetone-fixed slides were rinsed twice with PBS-T, and mounted in glycerol for examination. The tissues were viewed with a Zeiss LSM 510 scanning laser confocal microscope equipped with an argon/krypton laser. The distribution of spirochetes in the gut was determined by scanning the entire organ from end to end and throughout its depth at each point.

**Statistical analysis**

Results are expressed as the mean ± SE. The significance of the difference between the mean values of the groups was evaluated by Student’s t test or repeated-measure ANOVA with the Fisher protected least significant difference test with Statview software (SAS Institute, Cary, NC).

**Results**

**Characterization of OspA Abs**

The borreliacidal activities of OspA antisera and mAb were characterized so that the influence of these Abs on *B. burgdorferi*- *I. scapularis* interactions in vivo could be studied. C3.78 is an OspA mAb directed against *B. burgdorferi* N40 that can protect mice from *B. burgdorferi* N40 infection (16). We first determined that 0.4 µg/ml of mAb C3.78 was sufficient to kill the vast majority of *B. burgdorferi* N40 in vitro (Table I). As expected, we then demonstrated that antisera against OspA from *B. burgdorferi* N40 (OspA-N40), but not antisera against OspA from *B. afzelii* ACA-1 (OspA-ACA-1) or *B. garinii* ZQ-1 (OspA-ZQ-1), were able to kill *B. burgdorferi* N40 (Table I). Similar bactericidal activities of mAb C3.78 and OspA-N40 antisera were detected in our bactericidal assay when heat-inactivated serum was used (data not shown). Therefore, for the purpose of this study, we termed N40 Abs (mAb C3.78 and OspA-N40 antisera) as “borrelicidal” and non-N40 Abs (OspA-ACA-1 and OspA-ZQ-1) were termed as “nonborrelicidal.” Control antisera against OspF-N40 or ErpT-N40 (a *B. burgdorferi* gene expressed in vivo) did not have significant borrelicidal activity (Table I). However, antisera against OspA-ACA-1 or OspA-ZQ-1 were able to kill *B. afzelii* and *B. garinii* at dilutions of 1/3000 and 1/7000, respectively (data not shown). The borrelicidal effect of the Abs studied was determined both visually, by loss of motility, and was confirmed after an extended period of time by incorporation of [3H]adenine into dividing spirochetes.

In contrast to their strain-specific killing capacity, all of the OspA Abs were able to bind to OspA-N40. Each of the OspA antisera strongly stained *B. burgdorferi* N40 spirochetes as shown by immunofluorescence microscopy (Fig. 1A) and recognized recombinant OspA-N40 in ELISA to a dilution of at least 1/12,500 (Fig. 1B). Therefore, OspA-ACA-1 or OspA-ZQ-1 antisera effectively bound to, but did not kill, *B. burgdorferi* N40. Moreover, in a standard agglutination assay (34), neither of these OspA antisera resulted in appreciable agglutination of N40 spirochetes (data not shown).

![FIGURE 1](http://www.jimmunol.org/)  
**FIGURE 1.** Recognition of *B. burgdorferi* N40 and OspA-N40 by diverse OspA Abs. A, Immunofluorescence of *B. burgdorferi* N40 stained with OspA-N40 (lane 1), OspA-ACA-1 (lane 2), OspA-ZQ-1 (lane 3), or without primary antisera (lane 4). Spirochetes were fixed in acetone and labeled as described in Materials and Methods. All antisera were used at a 1/100 dilution. B, OspA Ab levels by ELISA. Recombinant OspA-N40 was probed with antisera to OspA-N40, OspA-ACA-1, and OspA-ZQ-1 (at 1/100, 1/500, 1/2,500, 1/12,500, and 1/62,500 dilutions). Data shown are OD450 (mean ± SE; n = 3).
OspA Abs inhibit association of spirochetes with the tick gut in vivo

We next examined whether B. burgdorferi N40 exposed to different OspA Abs could effectively colonize I. scapularis, particularly in cases where the Abs did not have borreliacidal activity. SCID mice were used in these studies because the animals cannot mount their own humoral response to B. burgdorferi during infection; thus, the effects of the administered Abs can be evaluated without the contribution of any acquired host response to the spirochete. Groups of three SCID mice were challenged with B. burgdorferi N40, and within 4 wk all the mice had developed visible swelling of the tibiotarsal joints (data not shown). Then OspA antisera (N40, ACA-1, or ZQ-1), mAb C3.78, control (OspF or ErpT) antisera, or PBS were administered to groups of animals. Twenty-four hours later, 10 uninfected ticks were allowed to feed to repletion on each mouse, and the engorged ticks were collected. Tick guts were dissected and the luminal contents examined for B. burgdorferi under dark-field microscopy. In ticks that fed on animals treated with OspA-ACA-1 or OspA-ZQ-1 antisera, control antisera, or PBS, viable B. burgdorferi were consistently detected (Fig. 2). For example, control (PBS-treated) slides (5 μl of tick content out of a total volume of 20 μl of tick content) contained 50 ± 8 spirochetes/ slide (or 200 spirochetes/tick). In contrast, spirochetes were not detected in guts of ticks that had fed on mice administered OspA-N40 antisera or mAb C3.78 (Fig. 2).

To determine whether specific OspA antisera could interfere with the ability of B. burgdorferi to adhere to the tick gut, we examined Borrelia-tick tissue associations at 24, 48, 72, and 96 h after tick engorgement. The tick gut diverticula were dissected, washed to remove unbound luminal contents, and examined by double-labeled confocal microscopy. B. burgdorferi in the control groups (PBS and OspF and ErpT antisera) were found in close proximity to the lumen of the nymphal tick gut (Fig. 3A and Table II). In contrast, OspA-ACA-1 or OspA-ZQ-1 antisera-treated samples had fewer spirochetes associated with the gut (Fig. 3A and Table II). Gut diverticula were devoid of spirochetes in samples treated with OspA-N40 antisera or mAb C3.78 (Fig. 3A and Table II). We then examined the persistence of the spirochetes in I. scapularis by allowing some groups of ticks to molt to the adult stage. The effects of borreliacidal and nonborreliacidal Abs were maintained at the adult stage (Fig. 3B).

Bactericidal OspA mAb C3.78 binds to OspAs with mutations in major gut binding epitope

To further differentiate the regions of OspA that are important in tick gut binding from the epitopes that bind to borreliacidal OspA (24, 25), we examined whether mAb C3.78, which we know binds to the borreliacidal epitope, could bind to recombinant OspAs with mutations in the tick gut binding domain, aa 229–247. Protective OspA mAbs such as C3.78 have been shown to bind to a conformational epitope in the carboxyl terminus of OspA and are sufficient to protect mice against B. burgdorferi infection (16, 25). Our previous work demonstrated that OspA aa 229–247 contain an epitope that is important in OspA-gut binding and that mutations in this region greatly reduced OspA-gut interaction (21). Therefore, we expressed several recombinant OspAs with such mutations in this area, including M4 (K231 to ΔA), M5 (V236–237 to ΔGS), and M6 (T242–244 to ΔANA) (21) and determined whether mAb C3.78 could bind to these OspAs. M5 and M6 have been shown previously to have reduced binding to the tick gut when compared with wild-type OspA (21). Wild-type OspA and a mutant OspA (M3) with an alteration in a different region of the protein (EVFK100–103 to ΔAVFA) that does not appear to be involved in spirochete-tick gut binding, served as controls. In a standard immunoblot, mAb C3.78 readily bound to wild-type or all the mutant OspAs (M4, M5, and M6) with alterations in the OspA-tick gut binding region (data not shown), suggesting that the important gut binding domain is distinct from the borreliacidal domain.

Discussion

B. burgdorferi display an array of different proteins on their outer surface throughout their life cycle, with OspA being prominently exposed within the tick vector (19). In general, B. burgdorferi express ospA in the gut of unfed ticks (8). ospA is repressed as spirochetes migrate from the tick and is not normally expressed by B. burgdorferi during murine infection (9, 18). ospA then is induced again as B. burgdorferi move from the mammalian host back into the arthropod vector (19). These temporal and tissue-specific observations suggest an important role for OspA within the tick, and it has been demonstrated that OspA facilitates B. burgdorferi-I. scapularis adherence in vitro (21). The current report used nonborreliacidal and borreliacidal OspA Abs to demonstrate the importance of OspA in spirochete colonization of the vector in vivo.

Antisera against OspA-ACA-1 and OspA-ZQ-1 were borreliacidal in vitro against B. afzelii ACA-1 and B. garinii ZQ-1, respectively (data not shown), but unable to kill B. burgdorferi N40 (Table I). As expected, OspA-N40 antisera were borreliacidal against B. burgdorferi N40. These results are consistent with prior reports on the genospecies-specific borreliacidal activity of OspA antisera, both in vitro and by in vivo passive immunization studies.
Borreliacidal OspA Abs. Images were recorded at ×630 magnification and are presented as a single image for clarity. B. burgdorferi (arrows) in adult ticks. Selected engorged nymphal ticks were allowed to molt to the adult stage and then were then examined for B. burgdorferi in a similar fashion. The representative images show that spirochetes did not flourish in the guts of tick that had been exposed as nymphs either to borreliacidal or non-borreliacidal OspA Abs. Images were recorded at ×400.

In general, diversity in the carboxyl terminus of OspA among B. burgdorferi sensu lato contributes to the inability of specific borreliacidal OspA Abs to bind diverse OspAs and the lack of cross-protective immunity. The selective borreliacidal capacities of these OspA antisera provide a framework for investigation of in vivo effects of such antisera on the interaction of B. burgdorferi N40 with I. scapularis.

Our in vivo studies examine the ability of nonborreliacidal OspA antisera to prevent effective tick colonization by B. burgdorferi. To assess the effect of host OspA Abs on B. burgdorferi entry to ticks, Abs were administered to B. burgdorferi-infected mice. OspA Abs transferred after initiation of infection do not protect from infection with B. burgdorferi, in part because the spirochetes down-regulate ospA in the host (9, 18). The influence of OspA Abs becomes apparent when the spirochetes express OspA as they reenter the tick (8). We used SCID mice in this study so that acquired humoral or cellular immune responses to B. burgdorferi during the course of infection could not influence B. burgdorferi within the vector. Our in vivo experiments demonstrate that OspA antisera effectively prevent B. burgdorferi from associating with the I. scapularis gut, even those that do not kill spirochetes. Viable, motile B. burgdorferi were found in ticks exposed to OspA-ACA-1 or OspA-ZQ-1 antisera during engorgement, showing that these antisera did not hinder B. burgdorferi from entering the vector. However, the OspA-ACA-1 or OspA-ZQ-1 antisera diminished the ability of the spirochetes to associate with the gut of the engorged ticks. In addition, markedly fewer B. burgdorferi persisted through the molt from nymph to adult ticks, further demonstrating that these antisera interfered with the ability of B. burgdorferi to establish infection within the arthropod.

OspA-ACA-1 and OspA-ZQ-1 antisera may affect B. burgdorferi in several ways. Epitopes on OspA that bind borreliacidal Abs vs those that bind tick gut epithelium are likely to be different. Mapping studies have shown that protective OspA mAbs, such as LA-2 and C3.78 bind to conformational epitopes within the carboxyl terminus of OspA (25, 35). At least one of the epitopes that

<table>
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<th>Antisera Transferred</th>
<th>Mean No. of B. burgdorferi/Field</th>
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<tr>
<td></td>
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<tr>
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<tr>
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<td>OspF-N40</td>
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* Mice were infected with B. burgdorferi before administration of selected OspA Abs or controls at 24 h before tick placement. Engorged ticks were examined from 24–96 h after detachment using confocal microscopy to enumerate B. burgdorferi in direct contact with tick gut tissue. In each experiment, the entire gut diverticulum was examined, and counts were made from at least three fields from two separate gut diverticula. The average number of microscopic fields/diverticula was 5.2; range, 2–7 fields/diverticulum. Data are the number of spirochetes per field from four independent experiments (mean ± SE). Differences between each of the individual OspA Ab-treated groups (OspA-N40, OspA mAb C3.78, OspA-ACA-1, or OspA-ZQ-1) with individual control groups (ErpT-N40, OspF-N40, or PBS) from 24 to 96 h were significant (p < 0.001). Statistical significance was determined by ANOVA and Fisher’s protected least significant difference test.
facilitates OspA-tick interactions is encoded within residues 229–247 (21) and we now have found that this region is not important for the binding of mAb C3.78, as these Abs bind to OspAs with mutations within residues 229–247. Nonborreliacidal OspA Abs may bind directly to the tick gut binding region, or alternatively, these Abs may bind to several epitopes of OspA on the B. burgdorferi surface and steric hindrance might then interfere with OspA binding to tick gut.

The mechanisms by which B. burgdorferi interact with the vector, and the influence of spirochete-tick interactions on the pathogenesis of infection remain to be fully explored. Certainly within the mammalian host, B. burgdorferi have different Ags that may serve similar functions. For example, B. burgdorferi decorin binding protein and fibronectin binding protein (BBK32) both facilitate the adherence of the spirochete to the extracellular matrix, albeit via different ligands (12, 13). Several B. burgdorferi ligands are probably involved in spirochete-tick gut interactions, and B. burgdorferi Ags that are preferentially expressed during the period of tick engorgement, such as OspC, BBK32, and BBK50 among others, may serve functions in the tick as well as the host. Ags differentially expressed during the blood meal help B. burgdorferi colonize the tick salivary glands (transiently) during the migration from the tick gut to the vertebrate host (33). Characterization of the I. scapularis ligands that interact with OspA and other B. burgdorferi Ags should increase our understanding of vector-B. burgdorferi interactions and suggest alternative protective strategies to interfere with pathogen transmission. Immunization of mice with the vector ligand for OspA or specific OspA peptides, could, theoretically at least, elicit Abs to prevent tick colonization by B. burgdorferi, and therefore interrupt the spirochete life cycle. Our current studies show that nonborreliacidal OspA Abs can block the adherence of B. burgdorferi to the tick gut and demonstrate the importance of OspA in spirochete-arthropod interactions in vivo.

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