Role of VlsE in host reinfection by the Lyme disease spirochete, *Borrelia burgdorferi*

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ABSTRACT

A key mechanism for immune evasion and persistent infection by the causative agent of Lyme borreliosis, *Borrelia burgdorferi* (Bb), is antigenic variation of the immunodominant VlsE surface protein. Although a multitude of other surface proteins exist that are immunogenic, VlsE is the only known Bb antigen that exhibits variation of its surface epitopes. A long-standing question regarding Bb immune escape has been how such a feat is accomplished through sequence variation of this single lipoprotein, despite the presence of a substantial number of additional antigens residing on the bacterial surface. In other bacterial pathogen systems, the dominant presence of surface-exposed variable proteins has been associated with the ability to reinfect a host. In the current study, we investigated whether host reinfection by Bb requires VlsE, and the likely mechanism involved. Host-adapted wild-type and VlsE mutant spirochetes were used to reinfect immunocompetent mice that had naturally cleared an infection with a VlsE-deficient clone. Our results demonstrate that VlsE is necessary for reinfection by Bb, and this ability is directly related to evasion of the host antibody response. Moreover, the data presented here raise the possibility that escape of Bb surface antigens from immune surveillance may involve epitope shielding by the VlsE protein.

INTRODUCTION

A substantial number of lipoproteins are present on the surface of Bb. However, only one surface-localized lipoprotein, VlsE, undergoes antigenic variation required for persistence (see figure below). How sequence variation of this single lipoprotein leads to immune evasion remains unknown. Surface epitope shielding and overriding of antibody response are proposed mechanisms whereby VlsE protects other surface antigens (1,6).

OBJECTIVE AND NOVELTY OF THE STUDY

Reinfection by Bb is clinically recognized in humans as well as other animals (3,4,5). In contrast, a number of experimental studies that employed murine models did not support it (2). Thus, the objective of our current study is to establish an experimental reinfection murine model and to examine a role of VlsE for host reinfection. The novelty of our experimental approach is that we assess capacity of Bb to evade host reimmunization using host-adapted (ha) clones. In addition, we, for the first time, generated a VlsE-complemented clone in cis (CVM), using a previously obtained VlsE knockout Bb mutant (Ko) (1).

METHODS AND RESULTS

Assessment of reinfection in immunologically naive and VlsE-experienced C3H mice

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Mouse infected via ip/sc with Ko*</th>
<th>Animal</th>
<th>SCID mice</th>
<th>SCID mice</th>
<th>Blood collected at day 7 post challenge with</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood (7)</td>
<td>4/4 5/5 5/5</td>
<td>I</td>
<td>Ko-specific sera Wt</td>
<td>3/3</td>
<td></td>
</tr>
<tr>
<td>Ear (28)</td>
<td>0/4 0/5 0/5</td>
<td>II</td>
<td>Wt-specific sera Ko</td>
<td>0/3</td>
<td>cVlsE</td>
</tr>
<tr>
<td>Blood (7)</td>
<td>4/4 0/5 0/5</td>
<td>IV</td>
<td>V</td>
<td>Preimmune sera Ko</td>
<td>0/3</td>
</tr>
<tr>
<td>Ears (28)</td>
<td>4/4 0/5 0/5</td>
<td>VI</td>
<td>VI sera cVlsE</td>
<td>3/3</td>
<td></td>
</tr>
</tbody>
</table>

*Values listed correspond to numbers of cultures positive/numbers tested.

**ha denotes host-adapted clone.

• Variant VlsE is necessary and sufficient for Bb to evade acquired humoral immune response during reinfection.

Is VlsE also required for spirochetes to avoid T-cell independent antibodies?

ACKNOWLEDGMENT

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REFERENCES


SUMMARY

VlsE is absolutely required for reinfection of mice by providing Bb with immune evasion from T-cell dependent antibodies.