Borrelia burgdorferi Pathogenesis and the Immune Response

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KEYWORDS

• Lyme disease • Genotypic variation • Adhesins • Type I interferon • Immune evasion

KEY POINTS

- *Borrelia burgdorferi* is highly invasive but does not produce any toxins. Lyme disease pathology is generally thought to be the result of host inflammatory response.
- There is substantial genotypic variation among *B burgdorferi* strains, and evidence suggests that certain strains have a greater probability of causing disseminated infection.
- *Borrelia burgdorferi* produces several adhesins that mediate binding to decorin, fibronectin, other glycosaminoglycans (GAGs), and integrins.
- Infection induces the synthesis of a variety of proinflammatory and antiinflammatory cytokines and chemokines by host immune cells that includes a type I interferon (IFNs) response that seems to depend on the genotype of the infecting *B burgdorferi* strain.
- The spirochete can evade the host immune response by resistance to complement-mediated killing facilitated by factor-H-binding proteins and by antigenic variation.

INTRODUCTION

Lyme disease, the most common vector-borne disease in North America and Europe,[1] is a multisystem disorder characterized by inflammation of affected tissues. Infection is initiated when spirochetes of the *B burgdorferi* sensu lato complex are deposited into the skin during the feeding of certain *Ixodes* ticks.[2] Some infections resolve at the site of inoculation, but if left untreated, skin-localized infection can progress to include distal target tissues following hematogenous dissemination of the spirochete.[3,4] The complex host-pathogen interactions that occur at the initial host-pathogen interface and determine the course of infection are likely influenced by multiple factors, including spirochete genotype, *B burgdorferi* proteins that mediate

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attachment and invasion, tick-derived components, host immune response, and *B burgdorferi* mechanisms of immune evasion. In this article, the authors review aspects of *B burgdorferi* pathogenesis and the host immune response to infection with regard primarily to *B burgdorferi* sensu stricto and host defenses at the initial host-pathogen interface in mammalian skin.

BORRELIA BURGDORFERI GENOMIC VARIATION

The genus *Borrelia* is composed of 2 major groups—the Lyme *Borrelia* and the relapsing fever *Borrelia*.[5] The Lyme *Borrelia* group contains 19 species, but only 4 (*B burgdorferi* sensu stricto, *Borrelia garinii, Borrelia afzelii,* and *Borrelia bavariensis*) cause human infection with any frequency.[5] In North America, the etiologic agent of virtually all Lyme disease is *B burgdorferi* sensu stricto (referred to hereinafter as *B burgdorferi*).

The *B burgdorferi* genome is unusual among bacteria in that it consists of multiple replicons. Whole genome sequencing of the type strain B31 revealed a 910-kb linear chromosome and 21 linear and circular plasmids.[6,7] Numerous studies involving a variety of molecular typing techniques established that there is substantial genotypic variation among *B burgdorferi* isolates.[8–14] This observation has been confirmed by whole genome sequencing of an additional 13 *B burgdorferi* isolates.[15] (It should be noted that as of this writing complete genome sequences, including all plasmids, are available for only 4 *B burgdorferi* strains—B31, N40, JD1, and ZS7; www.patricbrc.org). In addition to the chromosome, plasmids cp26 and lp54 and some cp32 replicons are present in all isolates.[13,16,17] The chromosome is essentially syntenic in all *B burgdorferi* strains except for minor variation at the right telomeric end, and the conserved portions are greater than 99% identical. The common 903-kb region of the chromosome encodes 815 putative open reading frames (ORFs) of greater than 50 amino acid residues and encompasses most of the housekeeping functions including metabolism, ion and nutrient transport, and information processing.[15,18]

By contrast, plasmid content among different *B burgdorferi* strains is quite heterogeneous, both with regard to the presence or absence of specific plasmid replicons and to sequence similarity[13,16,19]; this extensive heterogeneity has been confirmed by recent whole genome sequencing of multiple strains.[15,17] Plasmid content among 14 *B burgdorferi* isolates varied between 12 to 21 plasmids.[18] As a consequence, the putative number of ORFs varies from 1278 to 1521 among 4 fully sequenced *B burgdorferi* strains.[17]

Does this extensive genomic variation have implications for pathogenesis? The absence of certain plasmids results in reduced virulence in animal models of infection[20–23] or in ticks.[24–26] Wormser and colleagues,[27] using ribosomal spacer sequence typing, and Seinost and colleagues,[10] using outer surface protein C (OspC) typing, showed a significant association between the frequency of disseminated or invasive infection and certain *B burgdorferi* genotypes in patients with Lyme disease. This association was confirmed by subsequent studies with larger numbers of patients[28,29] and by multilocus sequence typing.[30] For example, a *B burgdorferi* genotype referred to as RST1/OspC type A was more frequently associated with disseminated infection in patients with Lyme disease.[10,27–29,31] The enhanced invasiveness of this genotype was confirmed in mouse infection studies.[32,33] More extensive whole genome sequencing of *B burgdorferi* isolates obtained from patients with Lyme disease is required to identify the genomic elements (genes, regulatory RNAs) that may be responsible for the variable pathogenic potential of different *B burgdorferi* genotypes.