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Characterization of a *Borrelia burgdorferi dnaJ* Homolog

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The gene encoding a *Borrelia burgdorferi* DnaJ homolog, located immediately 3′ of the *hsp70* gene, was characterized. Although there is a single copy of the *dnaJ* gene on the spirochetal chromosome, two distinct *dnaJ* transcripts are detected in *B. burgdorferi* RNA. RNA blot analysis indicates that the *dnaJ* gene can be transcribed alone or as part of a larger transcript containing the *hsp70* homolog.

We have been trying to determine how the spirochetal pathogen causing Lyme disease (*Borrelia burgdorferi*) interacts with the human immune system to produce the immune-mediated joint inflammation which is part of the clinical spectrum of Lyme disease (20, 21). Essential to this investigation is the characterization of spirochetal genes encoding immunoreactive proteins. Stress (or heat shock) proteins of a number of different bacterial and parasitic pathogens are major antigens recognized by the host humoral and cellular immune response to the infecting pathogen (19, 27, 28). We have previously characterized *B. burgdorferi* genes encoding immunoreactive proteins that are members of the Hsp60 (29) and Hsp70 (1) families of proteins. Another *Escherichia coli* heat shock protein, the DnaJ protein, which is required for cell viability at high temperatures, is involved in the replication of phage λ and bacterial DNA (25, 26) and in regulating protein phosphorylation (10) and degradation (22). The *dnaJ* gene forms an operon with the gene encoding the Hsp70 homolog (DnaK) in *E. coli* (for a review, see reference 6). DnaJ homologs have been found in mycobacteria (12), lower eucaryotes have multiple genes encoding DnaJ homologs (3, 17), and a human DnaJ homolog has recently been identified (24). In this paper, we present our initial characterization of the *B. burgdorferi dnaJ* gene.

Methods. DNA sequencing reactions were performed by using synthetic oligonucleotides as primers and the dideoxy method with modified T7 DNA polymerase (Stratagene, La Jolla, Calif.). The nucleotide sequence of the *dnaJ* gene was confirmed by sequencing an independently isolated genomic clone which contains the first 600 bp of *dnaJ* (data not shown). Translation of the DnaJ nucleotide sequence, alignment of the DnaJ amino acid sequences, and analysis of the secondary structures of the *hsp70* and *dnaJ* nucleotide sequences were performed by using PC/GENE computer software (Intelligenetics, Mountain View, Calif.).

Isolation of RNA from cultures of the CA12 and B31 strains of *B. burgdorferi* (1, 23) and RNA blotting (13) were performed as described previously. Purification of DNA from the B31 isolate of *B. burgdorferi* and DNA blotting were performed as previously described (1). Plasmids containing nucleotides 18 through 1076 of spirochetal *dnaJ*, nucleotides 1 through 1638 of *hsp60* (18), and nucleotides 1 through 1009 of *hsp70* (1) were radiolabeled with [α-^{32}P]dATP by random priming for use as hybridization probes (5).

Spirochetal *dnaJ* gene characterization. We have previously characterized two *B. burgdorferi* genomic DNA fragments containing portions of the spirochetal *hsp70* gene (1). Approximately 1 kb of spirochetal genomic DNA located 3′ of the *hsp70* gene was also contained within one of these fragments. *E. coli* and *Mycobacterium tuberculosis dnaJ* genes are located 3′ of the *hsp70* gene (12, 15). Therefore, as part of a systematic search for spirochetal genes encoding stress protein homologs, the nucleotide sequence of *B. burgdorferi* genomic DNA 3′ of the *hsp70* gene was determined. A 1,059-bp open reading frame immediately adjacent to the *hsp70* gene was noted. In contrast, *E. coli* and *M. tuberculosis dnaJ* genes are located 86 and 788 bp 3′ of *hsp70*, respectively (12, 15). Nevertheless, the chromosomal location and sequence homology of this spirochetal open reading frame indicate that it encodes a DnaJ homolog.

The nucleotide sequence of the *B. burgdorferi dnaJ* gene and its predicted amino acid sequence are presented in Fig. 1. The 1,059-bp open reading frame commences with a GTG (valine) initiation codon and terminates with a stop codon at nucleotides 1074 to 1076 (Fig. 1). Several features indicate that translation is initiated at this GTG codon (nucleotides 18 to 20): a 5-nucleotide ribosome binding site (Shine-Dalgarno sequence) is separated by 9 nucleotides from the GTG initiation codon, 8% of *E. coli* initiation codons are GTG, and AAA codons are very abundant second codons in procaryotic proteins (for a review, see reference 7). However, there were no sequences 5′ of *dnaJ* which resembled previously defined procaryotic promoter consensus sequences (4).

The protein encoded by the spirochetal *dnaJ* gene is predicted to contain 352 amino acids and to have a molecular mass of 39,169 Da. The encoded protein is very basic, containing 10 arginine and 45 lysine residues, with an estimated isoelectric point of 9.81. Alignment of the predicted amino acid sequence of the spirochetal DnaJ homolog with the *E. coli* (2), *M. tuberculosis* (12), and *Saccharomyces cerevisiae* (3) DnaJ protein sequences indicates that this spirochetal protein is a DnaJ homolog (Fig. 2). This amino acid alignment indicates that spirochetal DnaJ has 39.8, 34.4, and 37.5% identities with the *E. coli*, mycobacterial, and yeast DnaJ homologs, respectively. There is substantial amino acid homology between the bacterial and eucaryotic DnaJ homologs at the amino terminus, while they are most divergent at their carboxy termini. The spirochetal DnaJ homolog contains four cysteine-rich repeats located between Cys-148 and Gly-208 (Fig. 2), each with the Cys-X-X-Cys-X-Gly-X-Gly motif characteristic of DnaJ proteins. However, at position 155, spirochetal DnaJ has a lysine instead of

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 ----- HSP70 ----->|
 D  E  D  K  K  *  *
GACGAGGATAAAAAATAGTGAAAAAAGATTATTATGAAATTTTGGGGCTCTCAAAAGGAG   60
  -RBS-          V  K  K  D  Y  Y  E  I  L  G  L  S  K  G

CCTCAAAAGATGAGATAAAAAAAGCTTATAGAAAAATAGCAATTAAATATCACCCAGACA  120
A  S  K  D  E  I  K  K  A  Y  R  K  I  A  I  K  Y  H  P  D

GAAATCAAGGGAATGAAGAAGCCGCCTCTATCTTTAAAGAAGCCACTCAGGCTTACGAAA  180
R  N  Q  G  N  E  E  A  A  S  I  F  K  E  A  T  Q  A  Y  E

TTTTAATAGATGACAATAAAAAAGCTAAATACGACAGATTTGGGCATTCCGCTTTTGAAG  240
I  L  I  D  D  N  K  K  A  K  Y  D  R  F  G  H  S  A  F  E

GAGGAGGATTTGAAGGATTTTCAGGTGGATTTAGTGGATTTTCAGACATCTTTGAAGATT  300
G  G  G  F  E  G  F  S  G  G  F  S  G  F  S  D  I  F  E  D

TTGGCGATATTTTTGATTCATTTTTCACTGGAAACAAAGGACAAGAAAGAAATAGAAAAC  360
F  G  D  I  F  D  S  F  F  T  G  N  K  G  Q  E  R  N  R  K

ACGCAAAAGGTGAAGACTTGGGATACAACATAGAAATATCTCTTGAAAATGCATACTTTG  420
H  A  K  G  E  D  L  G  Y  N  I  E  I  S  L  E  N  A  Y  F

GGTACAAAAATAATATAAACATAGCAAGACAAATGCTCTGTGATTCTTGTCTCGGGAAAA  480
G  Y  K  N  N  I  N  I  A  R  Q  M  L  C  D  S  C  L  G  K

AATCCGAAAAAGGTACAAGTCCTTCGATATGTAACATGTGTAACGGCAGCGGAAGAGTAG  540
K  S  E  K  G  T  S  P  S  I  C  N  M  C  N  G  S  G  R  V

TACAAGGCGGAGGATTTTTCAGAGTTACAACAACATGTTCTAAATGTTACGGAGAAGGTA  600
V  Q  G  G  G  F  F  R  V  T  T  T  C  S  K  C  Y  G  E  G

AAATAATATCAAACCCTTGTAAATCCTGTAAAGGAAAAGGAAGTCTTACAAAGCAAGAAA  660
K  I  I  S  N  P  C  K  S  C  K  G  K  G  S  L  T  K  Q  E

CCATTCAATTAAACATTCCCCCAGGCATTGATAATAACCAACAAATAAAAATGAAAGGCA  720
T  I  Q  L  N  I  P  P  G  I  D  N  N  Q  Q  I  K  M  K  G

AGGGAAATGTTAATCCAGACAATCAAGAATATGGTGATCTTTATGTAAAAATATTGATAA  780
K  G  N  V  N  P  D  N  Q  E  Y  G  D  L  Y  V  K  I  L  I

GATCTCATAAAGTATTCAAAAGAAATGGTAAAGATCTCTATGCAATGCTTCCAATAAGCT  840
R  S  H  K  V  F  K  R  N  G  K  D  L  Y  A  M  L  P  I  S

TTACTCAAGCAGCGCTTGGAAAAGAAGTAAAAATAAAAACAATCGCTTCAAAAGAGATTA  900
F  T  Q  A  A  L  G  K  E  V  K  I  K  T  I  A  S  K  E  I

AAATACACATTCCAAAAGGAATAAACAATGAAGAACAAATTTTAATTAAAAATGCAGGGA  960
K  I  H  I  P  K  G  I  N  N  E  E  Q  I  L  I  K  N  A  G

TGCCAATTCTTCAAACCGAAAAGTTTGGAAATTTAATATTAATCACCAAAATAAAAACAC 1020
M  P  I  L  Q  T  E  K  F  G  N  L  I  L  I  T  K  I  K  T

CTAAAAATTTAAATTCTAATGCTATAAACTTTTTGAAAACTTGGGCAAAGAATTAA     1076
P  K  N  L  N  S  N  A  I  N  F  L  K  T  W  A  K  N  *
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FIG. 1. Nucleotide sequence and predicted amino acid sequence of the *B. burgdorferi* (CA12 isolate) *dnaJ* homolog. The predicted amino acid sequence at the carboxy terminus and termination codons of the adjacent *hsp*70 gene are indicated above the nucleotide sequence. A potential 5-nucleotide ribosome binding site (RBS) is also indicated. The four cysteine-rich amino acid sequence motifs are underlined.

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BBDNAJ      ------VKKDYYEILGLSKGASKDEIKKAYRKIAIKYHPDRNQGNEEAAS  44
ECDNAJ      MAKQ-----DYYEILGVSKTAEEREIRKAYKRLAMKYHPDRNQGDKEAEA  45
MTDNAJ      MAQREWVEKDFYQELGVSSDASPEEIKRAYRKLARDLHPDANPGNPAAGE  50
YDJ1        MVK----ETKFYDILGVPVTATDVEIKKAYRKCALKYHPDKNPSE-EAAE  45
                  ..*. **.. .*.  **..**.. * . *** *... .*..

BBDNAJ       IFKEATQAYEILIDDNKKAKYDRFGHSAFEGGGFEG------FSGGFSGF  88
ECDNAJ       KFKEIKEAYEVLTDSQKRAAYDQYGHAAFEQGGMGG--------GGFGG-  86
MTDNAJ       RFKAVSEAHNVLSDPAKRKEYDE-TRRLFAGGGFGGRRFDSGFGGGFGGF  99
YDJ1         KFKEASAAYEILSDPEKRDIYDQFGEDGLSGAGGAG-----GFPGG--GF  88
              **. ..*...* * .*.  **   .   .. .* .*       **  *

BBDNAJ      S----------DIFED--------FGDIFDSFFTGNKGQERNRKHAKGE 119
ECDNAJ      -----GADFS--DIF----------GDVFGDIF-G-GGRGRQ-RAARGA 115
MTDNAJ      GVGGDGAEFNLNDLFDAASRTGGTTIGDLFGGLF-GRGGSARPSRPRRGN 148
YDJ1        GFGDD----------------------IFSQFF-GAGGAQRPRGPQRGK 114
                                        .*. .* *  *  *     .*
                                        |------|          |----

BBDNAJ      DLGYNIEISLENAYFGYKNNINIARQMLCDSCLGKKSEKGTSPSICNMCN 169
ECDNAJ      DLRYNMELTLEEAVRGVTKEIRIPTLEECDVCHGSGAKPGTQPQTCPTCH 165
MTDNAJ      DLETETELDFVEAAKGVAMPLRLTSPAPCTNCHGSGARPGTSPKVCPTCN 198
YDJ1        DIKHEISASLEELYKGRTAKLALNKQILCKECEGRGKKGAV--KKCTSCN 162
            *.  . . .. .  *    . .     *. * *.    ..    *  *.
            --|                |------|        |------|

BBDNAJ      GSGR--VVQGGGFF--RVTTTCSKCYGEGKII--SNPCKSCKGKGSLTKQ 213
ECDNAJ      GSGQ--VQMRQGFF--AVQQTCPHCQGRGTLI--KDPCNKCHGHGRVERS 209
MTDNAJ      GSGV--INRMQGAF--GFSEPCTDCRGSGSII--EHPCEECKGTGVTTRT 242
YDJ1        GQGIKFVTRQMGPMIQRFQTECDVCHGTGDIIDPKDRCKSCNGKKVENER 212
            * *   .   * .        * * * *..*   ...*..*.*    .

BBDNAJ      ETIQLNIPPGIDNNQQIKMKGKGNVNPDNQEYGDLYVKILIRSHKVFKRN 263
ECDNAJ      KTLSVKIPAGVDTGDRIRLAGEGEAGEHGAPAGDLYVQVQVKQHPIFERE 259
MTDNAJ      RTINVRIPPGVEDGQRIRLAGQGEAGLRGAPSGDLYVTVHVRPDKIFGRD 292
YDJ1        KILEVHVEPGMKDGQRIVFKGEADQAPDVIPGDVVFI-VSERPHKSFKRD 261
             .. ... .*......* . *... .     . ... . . . * *.

BBDNAJ      GKDLYAMLPISFTQAALGKEVKIKTIASKEIKIHIPKG--INNEEQILIK 311
ECDNAJ      GNNLYCEVPINFAMAALGGEIEVPTLDGR-VKLKVPGE--TQTGKLFRMR 306
MTDNAJ      GDDLTVTVPVSFTELALGSTLSVPTLDGT-VGVRVPKG--TADGRILRVR 339
YDJ1        GDDLVYEAEIDLLTAIAGGEFALEHVSGDWLKVGIVPGEVIAPGMRKVIE 311
            *..*     ...     * .  .  ... . . .  .  .. .    .

BBDNAJ      NAGMPILQTEKFGNLILITKIKTPKNLNSNAINFLKTWAKN--------- 352
ECDNAJ      GKGVKSVRGGAQGDLLCRVVVETPVGLNERQKQLLQELQESFGGPTGEHN 356
MTDNAJ      GR-------------VCPSAV---------------------------- 347
YDJ1        GKGMPIPKYGGYGNLIIKFTIKFPENHFTSEEN-LKKLEEILP-PRIVPA 359
            .           .   .

BBDNAJ      ---------------------------------------------------  352
ECDNAJ      SPRSKSF-------FDGVK----------KFFDD-----------LTR  376
MTDNAJ      ----------------GVA----------ATY-------------LSP  356
YDJ1        IPKKATVDECVLADFDPAKYNRTRASRGGANYDSDEEEQGGEGVQCASQ  408
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FIG. 2. Alignment of the predicted amino acid sequence of the spirochetal DnaJ homolog (BBDNAJ) with the *E. coli* (ECDNAJ) (2), *M. tuberculosis* (MTDNAJ) (12), and *S. cerevisiae* (YDJ1) (3) DnaJ protein sequences. Positions where all three proteins have the same amino acid (*), positions with conserved amino acids (·), and locations of four cysteine-rich motifs (⊢−−⊣) are indicated. –, gap introduced into the sequence.

a glycine, which is present in the first cysteine-rich repeat of other DnaJ homologs.

One *dnaJ* gene, yet two RNA transcripts. The pattern of hybridization of the *dnaJ* probe to spirochetal genomic DNA indicates that there is a single copy of the *dnaJ* gene in the spirochetal genome (Fig. 3). We have previously localized the spirochetal *hsp*70 gene to the 950-kb linear duplex chromosome (1). Therefore, the spirochetal *dnaJ* gene, which is adjacent to the *hsp*70 gene, is also on the 95-kb chromosome.

The spirochetal *dnaJ* probe hybridized to two distinct transcripts present in *B. burgdorferi* RNA (Fig. 4). As previously demonstrated (1), *B. burgdorferi* RNA also contains two distinct *hsp*70 transcripts. The *hsp*60 probe hybridized to a single RNA transcript, indicating that the smaller *hsp*70 and *dnaJ* transcripts are not generated as a result of nonspecific degradation of the RNA (Fig. 4). Interestingly, an approximately 3-kb RNA transcript, sufficient in size to encode both proteins, hybridized to both the *hsp*70 and *dnaJ* probes (Fig. 4). This is the second example of two linked *B. burgdorferi* genes forming a common transcriptional unit. The genes encoding two *B. burgdorferi* outer surface proteins (OspA and OspB) are also transcribed from a common promoter, and the resulting RNA transcript encodes both outer surface proteins (9).

The *hsp*70 and *dnaJ* probes each hybridized to a second distinct RNA transcript. The size (approximately 1.2 kb) of the *dnaJ* transcript, which is smaller than either the 3-kb or the 2.2-kb *hsp*70 transcript, corresponds to the size of the

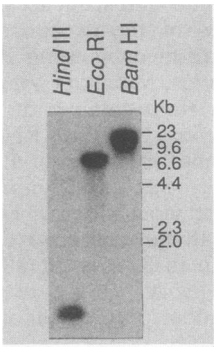

FIG. 3. Genomic-DNA blot analysis. Aliquots of *B. burgdorferi* (B31 isolate) DNA were digested with *Eco*RI (3 μg), *Bam*HI (3 μg), or *Hin*dIII (10 μg); electrophoresed in 1% agarose; blotted; and hybridized with a ^{32}P-labeled *dnaJ* probe. Sizes of DNA standards are shown.

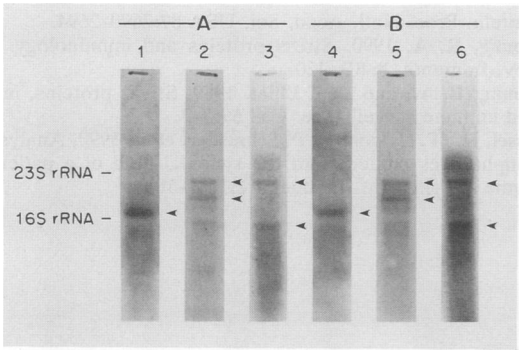

FIG. 4. The spirochetal *dnaJ* gene can be transcribed alone or as part of a larger transcript containing the *hsp*70 homolog. RNA prepared from the CA12 (A) and B31 (B) isolates of *B. burgdorferi* was hybridized to α-^{32}P-labeled *hsp*60 (lanes 1 and 4), *hsp*70 (lanes 2 and 5), or *dnaJ* (lanes 3 and 6) probes. Arrowheads, positions of the 23S (3.1-kb) and 16S (1.6-kb) rRNAs.

dnaJ gene. The possibility that the 2.2-kb *hsp*70 and the 1.2-kb *dnaJ* transcripts are generated from the 3-kb transcript by posttranscriptional processing has not been formally excluded. A very limited number of bacterial RNAs have been shown to undergo posttranscriptional processing (8, 11). However, this is less likely in light of the fact that the region of the spirochetal genome containing the *hsp*70 and *dnaJ* genes does not contain any intronic sequences. It is more likely that the three transcripts result from differential initiation and termination of transcription of the spirochetal *hsp*70 and *dnaJ* genes, as has been shown for other bacterial genes (14). A weak transcriptional termination sequence near the 5′ region of the *dnaJ* gene would cause some of the *hsp*70 transcripts to terminate before the *dnaJ* gene is fully transcribed, generating the 2.2-kb *hsp*70 RNA transcript. A computer analysis of the *hsp*70 and *dnaJ* sequences, examining their potential to form a hairpin loop structure, supports this possibility. Procaryotic transcriptional terminators have a common sequence motif consisting of a GC-rich region of dyad symmetry (16). The hairpin loop structure with the largest potential energy (−8.6 kcal [ca. −36,000 J]) was centered on nucleotide 54 of the *dnaJ* sequence. The smaller *dnaJ* transcript appears to be generated when the *dnaJ* gene is transcribed independently of the *hsp*70 gene. Therefore, the *dnaJ* gene can be transcribed alone or as part of a larger transcript containing the *hsp*70 homolog.

Nucleotide sequence accession number. The nucleic acid sequence of the spirochetal *dnaJ* gene is available through GenBank accession no. M97914.

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