Expression of HLA-B27 in Transgenic Mice Is Dependent on the Mouse H-2D Genes
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Summary

HLA-B27 transgenic mice in the context of various H-2 haplotypes were produced. A high expression of the HLA-B27 antigen was observed in mice homozygous for H-2b, H-2f, H-25, H-2p, H-2r, and H-2k haplotypes. Mice of the H-2° haplotype expressed HLA-B27 at an intermediate level. Expression of HLA-B27 was minimal in mice of the H-29 and H-2d haplotypes. This was observed both on the B10 background and in DBA/2 or BALB/c mice. Only minimal expression of HLA-B27 could be detected in B10.PL (K°D°) or B10.RKDB (K°S°D°L°) mice, indicating that the low level of HLA-B27 expression maps to the H-2D gene or a very closely linked gene. Integration and transcription of the HLA-B27 gene does not appear to be different between high-expressing haplotypes and low-expressing haplotypes as determined by Southern and Northern blot analysis. However, expression of HLA-B27 on the cell surface correlated with the amount of HLA-B27 and β2M that could be immunoprecipitated with an anti-B27 antibody. Therefore, the association of the B27 heavy chain with endogenous β2M and subsequent expression on the cell surface are disrupted in mice with some class I H-2D genes. Possible mechanisms that might contribute to this defect in assembly, transport, and expression of class I molecules are discussed.

The human MHC class I antigens HLA-A, HLA-B, and HLA-C consist of highly polymorphic 44,000-dalton heavy chains encoded by chromosome 6 (1) associated non-covalently with a 12,000-dalton light chain, β2-microglobulin (β2M) (2) encoded by chromosome 15 (3). In mice, the class I heavy chain is encoded by chromosome 17 (4) and β2M is encoded by chromosome 2 (5). The mouse class I MHC antigens H-2K, H-2D, and H-2L have similar structure and function as the human HLA-A, -B, and -C antigens (2, 6).

Based on studies with the human Daudi cell line and the murine R1 cell line, it appeared that β2M was required for expression of class I heavy chains (6–8). These cell lines have mutant β2M genes that do not synthesize β2M protein, and fail to express class I heavy chains on their cell surface even though they are readily detectable in the cytoplasm. Cell surface expression of class I proteins can be demonstrated in R1 or Daudi cells following fusion to cells that express normal mouse or human β2M (7, 8). Transferring β2M into Daudi cells also rescued expression of the class I proteins (9).

There may be exceptions to the requirement for β2M. The murine H-2Ld and H-2Db class I molecules do not appear to require β2M for cell surface expression (10–12). However, it has not been ruled out that β2M may bind to the H-2Db heavy chain during transport to the cell surface and then rapidly dissociate. A very low avidity of the Db heavy chain for β2M has been demonstrated (13).

Similarly, there appear to be differences in the affinity of human class I molecules for β2M. HLA-A5 and -B8 bind to β2M with high affinity, whereas HLA-A1, -A2, and -C bind to β2M with low affinity (14). The inefficient association of HLA-C heavy chains with β2M results in low expression of HLA-C at the cell surface (15). Therefore, association with β2M and subsequent expression vary for different class I heavy chains. Recent studies (16, 17) have demonstrated that peptides may be required for efficient association of class I heavy chains with β2M. Transacting factors may also play a role in cell surface trafficking. Differential requirements by class I antigens may explain why some class I heavy chains associate more efficiently with β2M and are expressed at higher levels on the cell surface compared with others.

It has been shown that mouse β2M can act as an effective substitute for human β2M. HLA-A, -B expression was observed in human–mouse hybrid cell lines independent of human β2M (18). On the other hand, the results in transgenic mice have not been so clear cut. Expression of HLA-B7 at the surface of transgenic spleen cells could be detected in the absence of human β2M; however, this expression was increased by the addition of human β2M (19).

Krimpenfort et al. (20) produced transgenic mice with two different HLA-B27 genes. Neither HLA-B27 gene product was expressed on the cell surface in these mice unless they were also transgenic for human β2M. We have produced transgenic mice expressing the HLA-B27 gene product on
the cell surface in the absence of human β2M (21). The reason for this discrepancy is unknown, but may be related to differences in the genetic make-up of mice used to produce the transgenic mice. To determine whether association of HLA-B27 with murine β2M and subsequent expression are affected by endogenous H-2 genes, the HLA-B27 transgene was introduced into mice with H-2<sup>a</sup>, H-2<sup>b</sup>, H-2<sup>c</sup>, H-2<sup>d</sup>, H-2<sup>f</sup>, H-2<sup>g</sup>, and H-2<sup>h</sup> haplotypes. We discovered that the level of HLA-B27 expressed on the cell surface varies with different H-2 haplotypes and maps to the D region of the MHC complex.

**Materials and Methods**

**Experimental Animals.** Mice transgenic for the HLA-B<sup>2</sup>i<sup>705</sup> gene were produced by microinjecting EcoRI fragments containing the entire B27 gene (courtesy of Dr. Helene Coppin, INSERM France) (22) into (B6 x SJL)<sub>f<sub>1</sub> mouse embryos that were implanted into pseudopregnant female mice. Two of the offspring (Nos. 1 and 5) were transgenic for the HLA-B<sup>2</sup>i<sup>705</sup> gene as determined by FACScan analysis and Southern blot analysis. The copy number of the B27 gene was 1-2 in founder mouse 5 and 7-8 in founder 1. Both of the founder mice were repeatedly backcrossed to mice on the B10 background. Progeny of founder mouse 1 were backcrossed to B10.S, B10.M, and B10.D2 mice producing B27 transgenic mice homozygous for H-2<sup>a</sup>, H-2<sup>b</sup>, and H-2<sup>c</sup>, respectively. Progeny of founder mouse 5 were backcrossed to B10, B10.S, B10.P, B10.SM, B10.PL, B10.RIII, B10.K, and B10.Q producing B27 transgenic mice homozygous for H-2<sup>a</sup>, H-2<sup>b</sup>, H-2<sup>c</sup>, H-2<sup>d</sup>, H-2<sup>f</sup>, H-2<sup>g</sup>, and H-2<sup>h</sup>, respectively. In addition, B27 transgenic mice homozygous for H-2<sup>d</sup> were produced by mating progeny of founder 5 to DBA/2 and BALB/c. HLA-B27<sup>+</sup> mice were mated to B10.RKDB (K<sup>e</sup>, F<sup>e</sup>, C<sup>e</sup>, D<sup>e</sup>, L<sup>e</sup>) to map the gene controlling the expression of HLA-B27. All the B27 transgenic mice used in these studies were in the fifth to eighth backcross generation.

**Fluorocytometric Analysis.** The ME1 antibody (anti-HLA-B7, B22, and B27) (23) was obtained from American Type Culture Collection (Rockville, MD). The ME1 culture supernatant was purified over a protein G column and biotinylated by standard procedure. PBMC were separated on Ficoll, washed in PBS containing 1% BSA and 0.05% sodium azide, then incubated with the biotinylated ME1. After washing in PBS buffer, the cells were incubated an additional 30 min with streptavidin conjugated to phycoerythrin (TAGO Immunologicals, Burlingame, CA). Cytocfluorometry was carried out using a FACS IV flow cytometer (Becton Dickinson & Co., Mountain View, CA).

**Southern Blot Analysis.** Genomic DNA was extracted from the tails of weaning mice and digested with PstI. The DNA was electrophoresed on 0.8% agarose gels and transferred in 6x SSC to Hybond-N nylon membranes (Amersham Corp., Arlington Heights, IL). The membranes were prehybridized with 6x SSC, 5x Denhardt's solution, 0.5% SDS, and 100 µg/ml denatured salmon sperm DNA at 65°C, then hybridized in the same buffer at 65°C with [32P]-oligolabeled 6.5-kb EcoRI fragments containing the B27 gene. The membranes were washed in 2x SSC for 10 min at 65°C, followed by a 10-min wash in 2x SSC, 0.1% SDS and then exposed to Kodak XAR film for 24 h at ~70°C.

**Northern Blot Analysis.** Tissue RNA was prepared by guanidine isothiocyanate extraction as described by Davis et al. (24). Total cellular RNA (30 µg) was electrophoresed in formaldehyde/agarose gels and transferred in 20x SSC to Hybond-N nylon membranes (Amersham Corp.). The membranes were prehybridized with 50% deionized formamide, 5x Denhardt's solution; 5x SSC, 0.1% SDS, and 100 µg/ml denatured salmon sperm DNA at 42°C, then hybridized in the same solution containing 2x Denhardt's and [32P]-oligolabeled 6.5-kb EcoRI-digested B27 fragments. Washes consisted of 2x SSC and 0.1% SDS at 43°C. Higher stringency washes of 0.1x SSC, 0.1% SDS at increasing temperatures were used as needed. The membranes were exposed to Kodak XAR film for 24 h at ~70°C. To determine levels of steady-state mRNA, membranes were stripped by sequential 10-min washes in: 0.1x SSC, 0.05 M NaOH, H<sub>2</sub>O, 20 mM TRIS, pH 7.4, and 5x SSC. The filter was then rehybridized to chicken actin probe (Oncor, Gaithersburg, MD) using the procedure described above.

**Immunoprecipitation.** Splenocytes (30 x 10<sup>6</sup>) were incubated for 4 h at 37°C with 30 ml of methionine-free RPMI 1640 (Gibco Laboratories, Grand Island, NY) media containing 5% FCS, 1 mM glutamine, 100 U each of penicillin and streptomycin, and 30 µCi/ml [35S]methionine (1,10 Ci/mmol; Amersham Corp.). Radiolabeled cells were solubilized at 2.5 x 10<sup>6</sup> cells/ml in 0.1 M Tris, 0.15 M NaCl, 0.5% Triton-X100, 1% Trasylol, pH 7.4, for 30 min at 4°C. Particular matter was removed by centrifugation. Lysates were preclarified by incubation with protein A-Sepharose (Sigma Chemical Co., St. Louis, MO) for 30 min at 4°C. The lysates were then incubated overnight at 4°C with purified ME1 antibody bound to CNBr-activated Sepharose 4B (Sigma Chemical Co.) at 25 µg/µl Sepharose. The immunoprecipitates were eluted from the Sepharose with 0.06 M Tris, 10% glycerol, 2% (wt/vol) SDS, 2-ME (5%), then boiled for 5 min and electrophoresed on SDS-containing 15% polyacrylamide gels. After fixation, the gels were treated with Amplify (Amersham Corp.) for 30 min, then with 10% acetic acid and 1% glycerol for 60 min. After drying, the gels were exposed to Kodak XAR film.

**Results**

**Expression of HLA-B27 and H-2 Haplotype.** There is a high level of expression of the HLA-B27 transgene in mice of the H-2<sup>d</sup> haplotype in association with mouse β2M. However, this expression was lower than that observed with human HLA-B27<sup>+</sup> cells (Fig. 1, A and B). Expression of the HLA-B27 transgene in mice homozygous for H-2<sup>a</sup>, H-2<sup>b</sup>, H-2<sup>c</sup>, H-2<sup>f</sup>, and H-2<sup>h</sup> was similar to that observed in HLA-B27 transgenic mice homozygous for H-2<sup>d</sup>. Surprisingly, when B10.HLA-B27 (H-2<sup>b/d</sup>) transgenic mice were mated to B10.Q (H-2<sup>q</sup>) strain, the level of expression of HLA-B27 was decreased in the offspring heterozygous for H-2<sup>b/q</sup>, as shown in Fig. 1 C. Further backcrossing to B10.Q showed that expression of the B27 transgene was barely detectable in mice that were homozygous for H-2<sup>d</sup> (Fig. 1 C). A similar phenomenon was observed when B27 transgenic mice from the B10.M (H-2<sup>d</sup>) line were mated to B10.D2 (H-2<sup>d</sup>) and when B27 transgenic mice from the B10.S (H-2<sup>s</sup>) line were mated to B10.SM (H-2<sup>s</sup>) (Fig. 2). Intermediate expression was observed in mice heterozygous at the H-2 allele (f/d or s/v), whereas minimal expression was detected in mice homozygous for H-2<sup>d</sup> or H-2<sup>s</sup>. Expression of HLA-B27 was also inhibited in mice homozygous for H-2<sup>n</sup> from the BALB/c or DBA/2 backgrounds. The B10.D2 transgenic mice originated from founder mouse 1, whereas all other lines discussed in this paper originated from founder mouse 5. Therefore, decreased expression relating to haplotype was observed in progeny from both original founder mice. Thus, B27
expression was high in strains that are homozygous for H-2\(^b\),\(k\),\(p\), and \(r\), low in strains of H-2\(^d\) and \(q\), and intermediate in H-2\(^v\) (Table 1).

**Mapping of the Low Expression Gene.** The lack of expression appeared to map to the D region of the MHC complex since decreased expression was seen in the B10.PL mice (K\(^d\)D\(^d\)) similar to H-2\(^d\) strains. Low expression was also observed in offspring of [B27 (b/d) \(\times\) B10.RKDB] mice with haplotype H-2\(^d\)/H-2K\(^k\)S\(^d\)D\(^d\)L\(^b\) compared with siblings with haplotype H-2\(^b\)/H-2K\(^k\)S\(^d\)D\(^d\)L\(^b\) (Fig. 3 B and Table 2). Thus, low expression maps in the chromosomal region to the right of C4 and left of L since crossing over in B10.RKDB occurred between D4\(^v\) and L\(^b\) (25). Further, the low expressor strains H-2\(^v\) and H-2\(^q\) have duplicated H-2D region genes similar to H-2\(^d\), while all the high expressor strains have only one D/L gene, presumably the L gene.

**Inheritance of the B27 Gene.** To determine whether the lower level of expression of HLA-B27 in certain haplotypes is due to an alteration of the integration of the gene into the mouse genome, Southern blot analysis was performed using DNA extracted from the tails of B27 transgenic mice of various haplotypes. No differences were observed in the number of gene copies or in the size of the expected bands after digestion with PstI between low expressing lines (B10.SM, B10.Q, B10.PL, BALB/c, DBA/2, and RKDB) and higher expressing lines (B10, b/RKDB) (Fig. 4). Results obtained with DNA from transgenic B10.M, B10.K, B10.P, B10.RIII, and B10.S mice originating from founder mouse 5 were similar to those using DNA from the transgenic B10 mice (data not shown). The expected bands were darker with DNA from transgenic B10.D2 mice originating from founder mouse 1, indicative of the higher gene copy number in these animals. Similar results were observed with transgenic B10.S or B10.M mice originating from founder mouse 1.

**Transcription of the B27 Gene.** RNA was extracted from the spleens of transgenic mice and negative littermates, and compared in Northern blot analysis to determine whether a transcriptional defect is responsible for the lower expression of HLA-B27 in certain haplotypes. The results from [(B27 (b/b) \(\times\) BALB/c) \(\times\) BALB/c], [(B27 (b/b) \(\times\) DBA/2) \(\times\) DBA/2], [(B27 (b/b) \(\times\) B10.Q) \(\times\) B10.Q], and from B27

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**Table 1. Expression of B27 and H-2 Haplotype**

| Strain | H-2 Haplotype | B27 Expression |
|--------|----------------|----------------|
| B10    | b/b            | +              |
| B10.D2 | d/d            | -              |
| B10.M  | f/f            | +              |
| B10.K  | k/k            | +              |
| B10.P  | p/p            | +              |
| B10.Q  | q/q            | -              |
| B10.RIII | r/r           | +              |
| B10.SM | v/v            | ±              |
| DBA/2  | d/d            | -              |
| BALB/c | d/d            | -              |

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Figure 3. Cell surface expression of HLA-B*2705 on PBL from (A) HLA-B27+ and HLA-B27− littermates on a B10.S background backcrossed twice to B10.PL (Dd) mice; (B) a transgenic HLA-B27 mouse heterozygous for H-2d/¢ backcrossed to B10.RKDB (DdLb). The haplotype of the H-2D region is indicated. The cells were stained with the anti-B27 antibody ME-1.

Table 2. Mapping Expression of HLA-B27

| Strain   | K Aa Ea C4 D D2 D3 D4 L Expression |
|----------|------------------------------------|
| B10      | b b b b - - - - b +                |
| B10.K    | k k k k - - - - k +                |
| B10.Q    | q q q q q q q q q q q -            |
| B10.SM   | v v v v v v v v v ? v -           |
| B10.D2   | d d d d d d d d d d -              |
| B10.PL   | u u u u d d d d d d -              |
| B10.RKDB | k k k k d+ d d d b -              |

*The genes that are implicated in the decreased expression of B27 are underlined.

Discussion

This study demonstrates that the HLA-B27 transgene is expressed at different levels on the cell surface in different haplotypes of mice. High expression of the HLA-B27 transgene was observed in mice homozygous for H-2b, H-2f, H-2d, and H-2q on the BALB/c background. In contrast, B27 transgenic mice homozogous for H-2d on the BALB/c or DBA/2 backgrounds (data not shown). Therefore, the decreased expression of HLA-B27 in H-2d, H-2f, and H-2q appears to be associated with less efficient association of the HLA-B27 heavy chain with the endogenous mouse β2M in these strains. Since β2M within MHC congenic mice should be identical, the class I H-2D region determines association of B27 with β2M and transport of the complex to the cell surface.
2; H-2\(^p\), H-2\(^q\), and H-2\(^v\) haplotypes. Intermediate expression was observed in mice of the H-2\(^q\) haplotype, whereas little or no expression could be detected in mice of H-2\(^d\) or H-2\(^q\) haplotypes. The level of HLA-B27 expression is controlled by the H-2D gene or a very closely linked gene since HLA-B27 expression was not observed in B10.PL (K\(^d\)) mice. The recombinant B10.RKDB maps the "low expression effect" to the left of the L gene to the chromosomal region H-2D1-D4. The decreased expression of HLA-B27 in certain haplotypes is a post-transcriptional event since the HLA-B27 DNA and RNA levels were similar in all of the transgenic haplotypes. The level of expression of HLA-B27 on the cell surface directly correlated with the amount of \(\beta_2\)M co-precipitated with the HLA-B27 heavy chains.

Varying levels of expression of HLA-B27 in transfected mouse cells have been demonstrated (22, 26-28). Some expression of HLA-B27 in P815 cells (H-2\(^d\)) has been observed (26-27). However, this cell line was originally described as a highly transfatable variant from the mouse mastocytoma P815 (29). The characteristic that allows this cell line to be transfected with a high efficiency may override, interfere with, or compensate for the ability of the H-2D molecule to inhibit cell surface expression of HLA-B27. Rein et al. (28) reported a lack of expression of HLA-B27 in transfected 3T3 (H-2\(^d\)) or L cells (H-2\(^v\)). However, the antibody used to detect cell surface expression in these experiments was W6/32, which does not bind well to human heavy chains complexed with murine \(\beta_2\)M (30). In contrast, expression of HLA-B27 in transfected L cells detected with the ME1 antibody has been described (22). Consequently, the influence of H-2 haplotype on expression of HLA-B27 in cell lines has not been clearly elucidated and awaits further experimentation.

The mechanism by which the H-2D molecules interfere with expression of HLA-B27 might reveal important events that occur during processing, assembly, and trafficking of class I molecules to the cell surface. One possibility is that competition with HLA-B27 for the endogenous mouse \(\beta_2\)M may be associated with the number of genes encoding functional antigen-presenting molecules in the D region of the murine MHC. The low expressor haplotypes d, q, and v have similar genetic lineage in the H-2D region. The H-2\(^d\) haplotype has duplicated H-2D regions expressing D and L genes as well as coding for D2, D3, and D4 pseudogenes (31). The H-2\(^q\) and H-2\(^v\) haplotypes also have duplicated D/L genes (32). While the H-2\(^d\), H-2\(^q\), and H-2\(^v\) haplotypes encode multiple "D/L" genes, the other haplotypes examined (H-2\(^p\), H-2\(^r\), H-2\(^s\), H-2\(^h\), H-2\(^d\), H-2\(^v\), and H-2\(^d\)) only contain a single "D/L" gene (32). Probes for H-2D\(^d\) and H-2L\(^d\) revealed H-2L\(^d\) related genes in several haplotypes but no H-2D\(^d\)-like genes in any of the other haplotypes. Consequently, H-2D\(^d\)-like genes and HLA-B27 could compete for \(\beta_2\)M. Further evidence for the competition for \(\beta_2\)M can be demonstrated if introduction of human \(\beta_2\)M into these strains rescues expression of B27 on the cell surface.

On the other hand, the competition between H-2D\(^d\)-like molecules and HLA-B27 may not be for \(\beta_2\)M per se, but for an endogenous peptide which controls the association of the class I heavy chains with \(\beta_2\)M. Salter and Cresswell (16) showed that class I heavy chains and \(\beta_2\)M do not associate in a variant B-LCLXTLCL hybrid, despite synthesis of normal amounts of each. They hypothesized that an additional molecule not present in the variant may be necessary for efficient assembly of class I molecules and \(\beta_2\)M. Studies by Townsend et al. (17) suggest that the association of peptides with the binding site of the class I heavy chain may be required for stable association and subsequent expression of the heavy chain with \(\beta_2\)M. Recent studies have shown that peptides increase the expression of L\(^d\) on the surface of a transfected L cell line (33). We can envisage a situation where similarity between the D\(^d\) and D\(^q\) molecules results in the usage of the same "self peptide," while the peptides used by other haplotypes are different. B27 may have the same binding site for the self peptides as D\(^d\) and thus may compete for that self peptide. Studies by Rebai et al. (34) demonstrating shared determinants on the H-2D\(^d\) and HLA-B27 molecules are consistent with this hypothesis. Artificial peptides can be used to see whether expression of B27 can be increased in these mice.

Another possibility is that there are transacting factors controlled by genes mapping within the MHC that influence processing, assembly, and trafficking of class I molecules. One of these genes may map to the D1-D4 interval that has a negative influence on the assembly and expression of the B27 molecule. Recently, Hosken and Bevan (35) have proposed a factor that has a chaperone-like (CHAP) function and retains class I molecule in the endoplasmic reticulum in the absence of peptide binding.

An intriguing possibility is that the events leading to the nonexpression of B27 in the H-2\(^d\)/\(^q\)/\(^v\) mice may be related to the linkage between B27 and reactive arthritis. Infection with Yersinia enterocolitica strain 0:8 WA removed of plasmid causes arthritis in DBA/2 mice (36). Recent studies in our laboratory have tentatively mapped the susceptibility gene to the H-2D\(^d\) region in the context of Mls-1 (Nickerson, C.L., K.L. Hogen, H.S. Luthra, and C.S. David, manuscript in preparation). Molecular mimicry may exist between H-2D\(^d\), HLA-B27, and bacterial antigens. In addition, Yersinia might have a "super antigen" that binds to H-2D\(^d\) and B27 and stimulates T cells.
cells with certain V\textsubscript{\beta} receptors, similar to the \textit{Mycoplasma arthritides} mitogen and Staphylococcal toxins that bind to class II molecules and stimulate self-reactive T cells (37, 38). This binding site may be identical to the binding site for self peptides required for assembly of B27 in the H-2\textsuperscript{d} strain. Studies are currently underway in our lab to test the various hypotheses. The HLA-B27 transgenic mice should serve as a good in vivo model to study processing, assembly, trafficking, and expression of class I molecules, as well as to decipher the role of B27 and H-2\textsuperscript{d} in Yersinia-induced arthritis.

We are grateful to Kristine Hogen for excellent technical assistance and Mary Brandt for typing the manuscript. We thank Dr. Michael Robinson for his help with the immunoprecipitations, and Drs. Harvinder Luthra and Kathleen Donovan for advice and support.

These studies were supported by National Institutes of Health grant AR-39875. C.L. Nickerson was supported by NIH training grant CA-09127.

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