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Identification of a Candidate Regulatory Region in the Human CD8 Gene Complex by Colocalization of DNase I Hypersensitive Sites and Matrix Attachment Regions Which Bind SATB1 and GATA-3

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To locate elements regulating the human CD8 gene complex, we mapped nuclear matrix attachment regions (MARs) and DNase I hypersensitive (HS) sites over a 100-kb region that included the CD8B gene, the intergenic region, and the CD8A gene. MARs facilitate long-range chromatin remodeling required for enhancer activity and have been found closely linked to several lymphoid enhancers. Within the human CD8 gene complex, we identified six DNase HS clusters, four strong MARs, and several weaker MARs. Three of the strong MARs were closely linked to two tissue-specific DNase HS clusters (III and IV) at the 3′ end of the CD8B gene. To further establish the importance of this region, we obtained 19 kb of sequence and screened for potential binding sites for the MAR-binding protein, SATB1, and for GATA-3, both of which are critical for T cell development. By gel shift analysis we identified two strong SATB1 binding sites, located 4.5 kb apart, in strong MARs. We also detected strong GATA-3 binding to an oligonucleotide containing two GATA-3 motifs located at an HS site in cluster IV. This clustering of DNase HS sites and MARs capable of binding SATB1 and GATA-3 at the 3′ end of the CD8B gene suggests that this region is an epigenetic regulator of CD8 expression. The Journal of Immunology, 2002, 168: 3915–3922.

A s thymocytes progress through development, they undergo induction and repression of a number of cell surface molecules. Changes in the expression of the CD4 and CD8 T cell surface glycoproteins best characterize the stages of ontogeny and ultimately define the two major lineages of mature T cells (CD4+CD8− or CD4−CD8+). Gene knockout studies with CD4 and CD8a have shown that the entire respective lineage does not develop (1, 2), making it likely that factors that regulate CD4 and CD8 expression also regulate the functional commitment of the cell. Therefore investigating the mechanisms controlling CD4 and CD8 expression should increase our understanding of thymocyte development.

CD8 can be expressed in mice and humans as an αα homodimer or an αβ heterodimer. Human CD8β can also be expressed as a ββ homodimer in transfected COS cells and transgenic mice (3). The CD8A and B genes, closely linked at a distance of ~36 kb in mice and 56 kb in humans (see Fig. 1), are coexpressed on most CD8+ T cells. The close linkage and coexpression of the CD8 genes suggest coordinate regulation. However, regulation is not always coordinated, particularly in cells which seem to be extrathymically derived, as subsets of human NK cells (4) and gut intraepithelial lymphocytes (IELs) (5, 6) express only the CD8αα homodimer.

Toward identifying cis-acting transcriptional regulatory elements in the CD8 loci, large fragments of genomic DNA have been used to make transgenic mice. A 95-kb human genomic fragment beginning ~25 kb upstream of the CD8B gene and containing the entire CD8B gene afforded developmentally correct expression on thymus-derived T cells in transgenic mice, indicating that CD8 lineage-specific regulatory sequences must be located within that fragment (7). Likewise, an 80-kb murine genomic fragment from 2 kb upstream of the CD8B gene to 25 kb downstream of the CD8A gene allowed appropriate expression in transgenic mice (8). The 80-kb murine genomic fragment contained four clusters of DNase hypersensitive (HS) sites (9) which were analyzed for enhancer activity in transgenic mice. One cluster at the 3′ end of the CD8B gene and two in the intergenic region had enhancer activity. The results indicate that there are separate elements for CD8 expression in the thymus vs the periphery, and possibly also for CD8α vs CD8β (9–13).

To locate regulatory regions within the human CD8 gene complex, we mapped the DNase HS sites which often colocalize with cis-acting transcriptional regulators. In addition, since many lymphoid gene enhancers are closely linked to matrix association regions (MARs) (14), we also undertook the mapping of MARs in the human CD8A and B loci. MARs, interspersed in genomes on the average of 50–100 kb, have been identified as specialized genomic sequences that tightly associate with the nuclear matrix, a RNA and protein containing fraction that remains after high salt
HUMAN CD8 CANDIDATE REGULATORY REGION BINDS SATB1 and GATA-3

Results

DNase hypersensitivity mapping

We had previously identified a tissue-specific DNase HS cluster upstream of the human CD8B gene (HS I) (7) and another in the last intron of the CD8A gene (HS VI) (40). The entire human CD8 gene complex was subchomed to facilitate a comprehensive mapping of DNase HS sites (Fig. 1). We determined that these clones

3916
contain the whole CD8 gene complex, except for a small region between clones 1231 and 1230 containing CD8β exon IX, which we obtained by PCR. Cell lines used in this work were HPB.All, which are a CD4+/CD8α–CD8β– thymoma cell line, and UC cells, a B cell line, as a control for tissue specificity. In the present work, we identified four additional DNase HS clusters in the human CD8 loci, making a total of six HS clusters (Fig. 1).

The data for DNase HS cluster III, located between CD8β exons VIII and IX, are shown in Fig. 2A. Of the seven bands marked, those at 3.7 and 3.4 kb appeared to be specific for HPB.ALL cells. The 5.6- and 4.5-kb bands can be seen in the UC cells in Fig. 2A, and bands appearing to correspond to the 3.4- and 4.2-kb bands were observed in other blots made from UC cells treated with 25 U/ml DNase (data not shown).

The data for DNase HS cluster IV and part of cluster V are shown in Fig. 2B. Of the bands seen, those at 4.7, 3.8, and 2.9 kb appeared to be specific for HPB.ALL cells, since those at 0.7, 0.5, and 0.4 kb were also seen in UC cells. These latter three small bands at the 3' end of 1230 have been placed in cluster V in Fig. 1 because they are closer to the other sites in cluster V than they are to the three tissue-specific DNase HS sites in cluster IV. There are several more weak DNase HS sites within cluster V, seen at 1.3, 1.0, 0.8, 0.5, 0.3, 0.25, and 0.1 kb from the 5' end of 1264 (data not shown). These bands, although weak, appear to be tissue specific.

There are several DNase HS sites within cluster II (Fig. 1 and data not shown). Sites which map to 1.5, 1.1, and 1.0 kb from the 3' end of clone 646 appear to be tissue specific, in that they were not seen in UC cells, whereas sites at 3.2 and 3.5 kb from the 3' end of 646 were also seen in UC cells. Cluster II contains additional sites, which map to 3.5, 3.0, 1.7, 1.6, 1.3, and 1.1 kb from the 5' end of 1229. Of these, only the 3.5-kb band appeared to be specific for HPB.ALL cells.

In summary, we identified four new DNase HS clusters in the human CD8 gene complex. These are DNase HS cluster II (HS II), located just downstream of CD8β exon VII, HS III, between CD8β exons VIII and IX, and HS IV and V, in the intergenic region, 3–5 and 8–11 kb downstream of CD8β exon IX, respectively. We also observed four weak but tissue-specific DNase HS sites 0–0.8 kb upstream of the first exons of both CD8α and CD8Bβ, in the promoter regions (Fig. 1 and data not shown).

**MAR assays**

An in vitro MAR-binding assay was used to map the MARs in the CD8 loci. Over the whole region, there were four strong MARs and several weaker MARs. In plasmid 1235-4, located 13–17 kb upstream of the CD8β gene, there is a strong MAR in the 5' 2-kb fragment and, in addition, at least one weaker MAR (Fig. 3A). Since the 0.9- and 1.6-kb fragments are juxtaposed, it is possible that there is only one MAR split between them. Another strong MAR, located between CD8B exons VIII and IX in fragment 1231, is shown in Fig. 3B. This strong MAR is closely linked to the tissue-specific DNase HS sites in cluster III (Fig. 4A). There is also a weaker MAR at the 5' end of clone 1231. The data for clone 1230, shown in Fig. 3C, indicate a cluster of MARs in the center of clone 1230.
of plasmid 1230, with two strong MARs flanking a weaker one. Two of the three tissue-specific DNase HS sites of cluster IV are located within the weak MAR and the third is within the strong MAR on the 3’ end of 1230 (Fig. 4B). We found six additional weaker MARs in the CD8 complex (data not shown). Thus, distributed over the CD8 gene complex were 4 strong MARs and 10 weaker MARs, as indicated in Fig. 1.

Sequence analysis

Given that MARs are generally AT-rich sequences, we considered whether this frequency of MARs could be attributed to the human CD8 genes possibly being located in an AT-rich isochore, as was the case for the 15q11-13 imprinting center (35). We determined the isochore type to which the CD8 genes belonged by manually scanning the third base of each codon in the coding regions for guanine cytosine (GC) content (percent GC3). CD8A and B genes were grouped into their corresponding isochores based on the following criteria: L1, GC poor (GC3 ≤ 57%), H1, GC high (57% < GC3 < 75%), and H3, GC rich (GC3 ≥ 75%) (41, 42). The GC3 content of the CD8A and B genes were 71 and 84%, placing them well into the GC high and GC-rich isochores, respectively (data not shown). This indicates that the frequency of MARs we observe is not simply due to location of the CD8 genes in an AT-rich isochore.

Since clones 1231 and 1230 contain strong MARs closely linked to tissue-specific DNase HS sites, we considered them likely candidates for containing regulatory elements. Therefore, we sequenced the 19 kb spanned by the plasmid 1231, plasmid 1230, the PCR product between 1231 and 1230, and 4 kb from the 5’ end of 1264. We located the CD8β exons VIII and IX within this region as shown in Fig. 1.

The sequence of a typical MAR is ~65% AT rich (43) and contains a region of 150–200 bp that has a high potential for base unpairing (44–46). A Thermodyn analysis of the 19-kb sequence predicted seven potential LFE regions (Fig. 4). Only one of the seven LFE regions did not localize to the biochemically determined MARs.

A mapping of repetitive elements in clones 1231 and 1230 is shown in Fig. 4. There were eight whole or partial Alu elements. Interestingly, five of the six long interspersed nuclear elements were within fragments that bound to the nuclear matrix. The strong MAR in 1231 overlapped on its 5’ end with a Tigger 1 element, an interspersed repeat that resembles DNA transposons, which move by excision and reintegration into the genome without a RNA intermediate.

Several sequence motifs have been associated with MARs (17, 37, 44, 47–49). We mapped ATATTT and vertebrate topoisomerase sites and found that there was some clustering in the biochemically defined MARs, but this clustering was not absolute, particularly for the topoisomerase (Fig. 4, A and B). In addition, we analyzed the sequence for potential SATB1-binding sequences. SATB1 is an interesting MAR-binding protein in that it does not recognize a DNA sequence but rather it is believed to recognize ATC sequences indirectly by the altered sugar-phosphate backbone determined by the ATC sequence context (50). The ATC enzymes, that were tested for MAR activity. The relative binding ratios (RBR) of the fragments within each assay are indicated beneath the restriction maps. Quantitation of some bands was not possible if they were not well resolved from other bands on the gel. Strong and weaker MARs are indicated in these maps by dark and light shading, respectively. B and C, A compilation of the locations of the MARs is shown at the bottom. C, An additional analysis using BamHI/BglI-digested plasmid 1230 as probe is not shown.
sequence defined by one strand consists of exclusively As, Ts and Cs, excluding Gs, and at least 65% AT content. When the ATC stretches are clustered, it potentially confers high base unpairing propensity (44). With only one exception, the long ATC sequence stretches within our 19-kb sequence were confined to regions containing MARs (Fig. 4).

SATB1 binding

To test for SATB1 binding to the potential ATC sequence stretches, we performed EMSAs using recombinant GST-SATB1. Ten fragments, ranging in size from 190 to 580 bp, and a control fragment were tested. Two fragments from the regions with strong matrix binding activity were found to bind purified SATB1. One fragment, from plasmid 1231, showed very strong binding (Fig. 5B) with a $K_d$ of 0.04–0.15 nM. A fragment from plasmid 1230, bound SATB1 more weakly with a $K_d$ of 1.6–2 nM (data not shown). Locations of these SATB1 binding sites are mapped in Fig. 4. For comparison, the $K_d$ values were 0.3–1 nM for in vitro SATB1 binding to six other MAR probes, including fragments from the IgH and /H9252 globin MARs, (51) and ranged from 1 to 29 nM for 16 SATB1-binding sequences identified using chromatin immunoprecipitation studies with anti-SATB1 Ab and T cell nuclear extracts (39).

Both SATB1 binding sites are in Thermodyn predicted LFE regions, which is consistent with previous findings that SATB1 binds to DNA regions with a high propensity to base unpair (52). In the very high-affinity binding fragment from 1231, there are 3 stretches of ATCs of 28, 31, and 27 bases, separated by 8 and 18 bases, respectively (Fig. 5C). Our other SATB1-binding site had two stretches of ATCs of 37 and 33 bases, separated by 33 bp (Fig. 5D). The presence of multiple potential SATB1 sites separated by 25 bp or less has been noted in other fragments that bound SATB1 (39).

GATA-3 binding

Another transcription factor that is potentially important for CD8A gene expression is GATA-3. We therefore analyzed the 19-kb region for putative GATA-3 sites using either the motif GATA or GATC with appropriate 5'H and 3'H bases according to Ko and Engel (53). We tested eight oligonucleotides for GATA-3 binding by EMSA analysis. We focused on oligonucleotide 5 with two tandem GATA-3 binding sites separated by 3 bases, that was located at a tissue-specific HS site. This oligonucleotide gave a band that was

![Figure 4](http://www.jimmunol.org/)

**FIGURE 4.** Sequence analysis of clones 1231 (A) and 1230 (B). The top of this figure shows the locations of the MARs as determined in Fig. 3. Dark and light shading indicate strong and weaker MARs, respectively. Locations of DNase HS sites, as determined in Fig. 2, are shown. Sites indicated with arrows are tissue specific. The (A + T) content is indicated and the locations of consensus MAR motifs are shown below. Sequences tested for SATB1 binding met the following criteria: a stretch of A/T/C greater than or equal to 30, well mixed, with AT content at least 65%, and second stretch of A/T/C greater than or equal to 20, with the two stretches not 35 bp apart. In addition, several longer single stretches of at least A/T/C were also tested since these may contain a weak binding site. Also shown are possible base unpairing regions, with predicted LFE, as determined by Thermodyn analysis (see Materials and Methods). This is followed by specific repetitive elements. B, The interruption of a line element with a very GC-rich insertion is shown with a vertical black oval.

![Figure 5](http://www.jimmunol.org/)

**FIGURE 5.** SATB1 selectively binds with high affinity to a fragment of the strong MAR of clone 1231. Gel mobility shift assays were performed with GST-SATB1 protein and, as a negative control, a 190-bp BsrGI fragment (A) or a contiguous 300-bp BsrGI-EcoRV fragment (B), both from clone 1231. DNA-binding activity was visualized after electrophoresis through a 6% acrylamide gel followed by autoradiography. Lanes 1–5 contain 0, 1.2, 0.3, 0.15, and 0.04 nM GST-SATB1 protein. The ATC sequence context from the 1231 MAR fragment which bound SATB1 is shown in C, with the potential SATB1 binding sites, stretches of As, Ts, and Cs, in bold and underlined. The ATC sequence context of the fragment from the strong MAR of 1230 which bound SATB1 is shown in D (see text).
shifted with an anti-GATA-3 Ab. A mutated oligonucleotide with the AGATAA site mutation, M1, was able to compete fairly well as compared with the wild-type oligonucleotide (Fig. 6A), indicating that the M1 site was not as critical for GATA-3 binding as the AGATAA site which when mutated (M2 mutant) could not compete. To test the other oligonucleotides, we performed cold competition studies (Fig. 6B). Oligonucleotide 7, with three potential GATA-3 sites, competed strongly and the others to a lesser extent. The IL-5 promoter oligonucleotide, which contains a known double binding site for GATA-3, competed for binding less well than did oligonucleotide 5. This may have to do with the arrangement of the two GATA-3 sites in both oligonucleotides. In contrast to the tandem GATA-3 sites in oligonucleotide 5, the two GATA-3 sites in the IL-5 GATA-3 oligonucleotide overlap and are on opposite strands. Interestingly, oligonucleotide 7 is located 400 kb 3’ of oligonucleotide 5 within the same MAR. This oligonucleotide, as well as oligonucleotides 2a, 2b, and 3 showed supershifts with the anti-GATA-3 Ab (data not shown).

**Discussion**

Gene transcription is dictated by regulatory elements to which transcription factors bind and by appropriate chromatin modification (epigenetic regulation). Because chromatin remodeling appears to be a critical component of gene transcription, DNase I HS sites, indicators of relatively open chromatin, are often used as signposts for regulatory elements. However, not all HS sites contain regulatory elements. Another indicator is colocalization of matrix attachment regions with HS sites. For example, there is a single MAR adjacent to both the IgL chain enhancer, (33) and the TCRβ enhancer (54). Also, MARs flank both the IgH (55) and the TCRα (56) enhancers. Therefore, identifying regions of the human CD8 locus that contain HS sites near MARs seemed a logical approach to more rapidly identify strong candidates for regulatory elements.

By mapping DNase I HS sites and MARs in the human CD8 gene complex, we found two regions at the 3′ end of the CD8β gene in which both HS sites and strong MARs were colocalized. The tissue-specific DNase I HS cluster III, located between the last two CD8β exons, was adjacent to a strong MAR. Another tissue-specific HS cluster, IV, located 3′ of the last exon, was flanked by strong MARs. Further support for the potential importance of these regions in CD8 gene expression is the presence of a very strong SATB1 binding site in the MAR linked to HS cluster III and another site in the 5′ MAR linked to HS cluster IV. Although we have discussed these regions separately, they encompass an 11-kb region that may actually function as a locus control region-like regulatory unit.

Positive functional effects by MARs on enhancer activity have been observed (56–60). Studies have shown that MARs are required for demethylation of the Igκ locus (61, 62) and generation of long-range accessibility of chromatin in the Igκ locus (15, 63). An elegant study by Forrester et al. (16) demonstrated that MARs could facilitate long-range chromatin remodeling. They studied the Igκ enhancer, which is flanked by MARs, for its ability to activate the Vκ promoter over a distance of 150 bp or 1.2 kb upstream of a methylated or demethylated gene in stable transfectants of B cell lines. They found that the enhancer alone induced local chromatin remodeling, giving rise to a DNase I HS site and local demethylation, which was sufficient to activate transcription when the enhancer was 150 bp from the promoter. However, for enhancer-mediated promoter activation over a distance, both MARs were required for methylated μ gene expression. The MARs in combination with the μ enhancer could induce acetylation of histones at a distal position. This may explain why the μ MARs were found to predominantly function in germline transmission but not in transient transfection assays where chromatin remodeling does not need to occur (60). Because the HS sites linked to the strong MARs that we have identified are located at least 20 kb from either CD8 promoter, it is possible that the MARs associated with these putative enhancers could promote a similar long-range interaction.

The higher order chromatin structure that may be required for tissue-specific expression of the CD8 genes may in part be regulated by the presence of SATB1. SATB1-binding sequences isolated from a T cell line were localized to the nuclear matrix at the base of chromatin loops in vivo (39). However, in a breast cancer cell line, in which SATB1 is absent, this was not the case for at least one of these SATB1-binding sequences, indicating that in vivo, anchoring of certain MARs onto the nuclear matrix is cell
type specific. The hypothesis was put forth that SATB1 binding to the base of chromatin loops in vivo would create a specific chromatin loop domain structure that was involved in T cell-specific gene regulation. The SATB1-binding MARs in the CD8 region may likewise form a chromatin loop structure that is tissue specific. The very high-affinity SATB1 binding site in the strong MAR located in the last intron of the CD8B gene and the other site in the strong MAR located 4.5 kb downstream could lead to the formation of a loop domain that might facilitate CD8 gene expression, possibly through long-range histone acetylation of the CD8 gene. Because of the differences in affinity for SATB1 between the two sites, the formation of specific loop structures may vary depending on the concentration of SATB1.

The other protein that we found to bind to the candidate regulatory region, GATA-3, is also likely to affect CD8A gene expression. In the mouse a region in the murine HS cluster II located 4–5 kb upstream of the CD8A gene (32) contains two GATA-3 binding sites which function in in vitro assays. These GATA-3 binding sites are within the murine CD8 gene thymocyte-specific enhancer which also contains a SATB1-binding MAR (64). Interestingly, GATA-3 levels are high in CD4/CD8 thymocytes and then decline as they mature (65). Therefore, GATA-3 may be most important for CD8 expression in the double-positive T cell stage and would bind to the thymocyte-specific enhancer. The strong GATA-3 binding site that we found in the human CD8 tissue-specific HS cluster IV is potentially a functional site in that it has two GATA motifs 3 bp apart; double GATA motifs are often found in functional GATA sites.

Although it would be very informative to be able to compare the location of HS sites between the two species, exact comparisons are not possible because the human gene complex has ∼20 kb more DNA in the intergenic region (56 kb) compared with the murine region (36 kb), and the murine CD8B gene lacks exons VIII and IX. Despite this caveat, some sites may be comparable (Fig. 7). For instance, the murine HS cluster IV at the end of the murine region (36 kb), and the murine CD8B gene (32) contains two GATA-3 binding sites which function in in vitro assays. These GATA-3 binding sites are within the murine CD8 gene thymocyte-specific enhancer which also contains a SATB1-binding MAR (64). Interestingly, GATA-3 levels are high in CD4/CD8 thymocytes and then decline as they mature (65). Therefore, GATA-3 may be most important for CD8 expression in the double-positive T cell stage and would bind to the thymocyte-specific enhancer. The strong GATA-3 binding site that we found in the human CD8 tissue-specific HS cluster IV is potentially a functional site in that it has two GATA motifs 3 bp apart; double GATA motifs are often found in functional GATA sites.

Another murine regulatory region, associated with DNase HS clusters II and IX, located in the intergenic region ∼16 kb upstream of the murine CD8B gene, contained an enhancer that was specific for mature CD8+ T cells and CD8α+IEL (10, 11). A fragment from murine DNase HS cluster II, just upstream of the murine CD8B gene, when analyzed alone did not display enhancer activity, but did direct expression to double-positive thymocytes when combined with cluster III (9). The location of human DNase HS clusters III, IV, and V in the intergenic region may be similar to these murine HS clusters in the intergenic region (8). The finding that one of the murine clusters did not function unless linked to another cluster indicates that a large regulatory unit composed of multiple HS clusters is likely to be regulating murine CD8A gene expression.

To address the functional significance of potential regulatory elements in the human CD8 gene complex, we have continued to test in transgenic animals portions from the 95-kb genomic CD8 fragment that gave tissue-specific expression in transgenic animals. Focusing on the region described in this article, we have linked cluster III plus MAR or clusters IV and V plus MARs to a genomic human CD8A gene marker gene and analyzed for expression in transgenic animals. High level expression in a small percentage of the murine CD8 T cells was noted with both constructs in all transgenic lines (two to five lines per transgene, our unpublished data). However, our failure to obtain expression in most of the murine CD8 T cells may be related to the fact that both regions together may be required for large numbers of cells expressing the transgene. Such studies are currently in progress.

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