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SATB1 regulates β-like globin genes through matrix related nuclear relocation of the cluster

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ABSTRACT

The nuclear location and relocation of genes play crucial regulatory roles in gene expression. SATB1, a MAR-binding protein, has been found to regulate β-like globin genes through chromatin remodeling. In this study, we generated K562 cells over-expressing wild-type or nuclear matrix targeting sequences (NMTS)-deficient SATB1 and found that like wild-type SATB1, NMTS-deficient SATB1 induces out loop of β-globin cluster from its chromosome territory (CT), while it is unable to associate the cluster with the nuclear matrix as wild-type SATB1 does and had no regulatory functions to the β-globin cluster. Besides, our data showed that the transacting factor occupancies and chromatin modifications at β-globin cluster were differentially affected by wild-type and NMTS-deficient SATB1. These results indicate that SATB1 regulates β-like globin genes at the nuclear level interlaced with chromatin and DNA level, and emphasize the nuclear matrix binding activity of SATB1 to its regulatory function.

Introduction

Accumulating evidence showed that the nucleus is well organized, where each chromosome occupies distinct nuclear position and forms discrete entity termed chromosome territory (CT) [1]. Previous studies suggested that the localizations of genes relative to their CTs are regulated in correspondence with their activities [2,3]. The human β-globin gene cluster is a paradigm for further studying the mechanisms of gene regulation at nuclear level. This cluster locates at the short arm of chromosome 11 and consists of five developmental stage specific genes—embryonic (ε), fetal (Gγ, Aγ) and adult (δ, β) globins, and a powerful far upstream locus control region (LCR) which comprises five DNase I hypersensitive sites (HSs). In erythroid cells, the β-globin locus is looped out from its CT even before transcriptional induction [4] indicating that the extrusion should be considered as a poised state prior to activation rather than a consequence of transcription.

In nuclei, chromatin fibers are organized into loops (5–200 kb) by attaching the structural constraints at their bases—the nuclear matrix. Besides being a skeleton, nuclear matrix is also considered as platform for regulatory factors. Recent studies suggested that matrix/scaffold attachment regions (MARs/SARs) bind with matrix in a discriminatory manner and the selecting process depends on the structural and functional requirements of the cell [5]. SATB1 (special AT-rich binding protein 1), a MAR-binding protein, has been considered to be a new type of gene regulator. It provides docking sites for specialized DNA sequences and enzymes to regulate gene expression over long distances [6–8]. Amino acids 224–278 of SATB1 make up of a nuclear matrix targeting sequence (NMTS) and are important to the formation of the unique birdcage-like structure of SATB1 [9,10].

Previous study showed that over-expression of SATB1 in K562 cells increased ε-globin gene expression and decreased γ-globin gene expression by remodeling chromatin states [11]. Our recent work suggested that SATB1 is the critical component of an "inter-MAR association", which contributes to the transcriptionally active looping events in human β-globin gene cluster [12]. In this report, we further investigated the mechanism through which SATB1 regulated the expression of the cluster. Functional significance of its nuclear matrix targeting character of SATB1 was further addressed by observing the effects of wild-type and the NMTS-deficient-SATB1 on the expression and nuclear positioning of β-globoin gene cluster.

Materials and methods

Cell culture. Human erythroleukemia K562 and HeLa cells (PUMC Culture Collection) were cultured in RPMI 1640/10% FBS. Induction of K562 cells were carried out under 50 μM hemin for 72 h.

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Plasmid construction. The SATB1 expression vector-pEGFP/SATB1 was constructed by amplifying SATB1 cDNA from pE-CHAT1146 via PCR [13], ligating it into pEGFP-N2 (Clontech, Palo Alto, CA). The NMTS-deletion SATB1 expression vector-pEGFP/mSATB1 was constructed via recombinant PCR. Briefly, two fragments were separately amplified from the SATB1 cDNA with primer pair1 and pair2 (see Supplementary Material). The NMTS was deleted in the second step PCR with primer A and D using the mixture of products from the two first step PCRs as a template. The product of the second step was ligated into pEGFP-N2 to give rise to pEGFP/mSATB1. The sequence accuracy of the two plasmids was confirmed by DNA sequencing. Stably transfected cell lines were generated through introducing pEGFP/SATB1 or pEGFP/mSATB1 into K562 cells by Lipofectamin 2000 and selected with geneticin.

Halo preparation. Nuclear halos were prepared essentially as described [5].

DNA FISH. Two dimensional FISH was performed as described [14]. Human chromosome 11 paint was from Cambio (Cat. No. 1066-11B-02–1). BAC probe for human β-globin cluster was nick translated by DIG-Nick translation Mix (Roche, Germany), using BAC186D7 as the template [15]. Chromosome paints were used according to manufacturers' recommendations with 100–200 ng of BAC probes. Positions of BAC probes with respect to CTs and nuclear matrix were scored in Adobe Photoshop. The looping frequency for each cell line is equal to [extruded β-globin cluster/total β-globin cluster scored]. The matrix-associated frequency was equal to [associated β-globin cluster/total β-globin cluster scored]. χ^2 test was used for statistically analysis and the threshold of statistical significance was $P < 0.05$.

Chromatin immunoprecipitation. Chromatin extracts were prepared as described previously [16] with minor modifications in our lab [17]. Antibodies against RNA Polymerase II (Pol II) and GATA1 were purchased from Santa Cruz biotechnology, Inc. (USA). Antibodies against acetylated H3 and H4 were obtained from Upstate biotechnology (Lake Placid, NY). GAPDH was used as internal control.

Results

To investigate the influence of SATB1 on globin gene expression and further explore the related regulatory mechanism, we generated stably transfected K562 cells with wild-type or NMTS-deficient SATB1 overexpression called SATB1/K562 or mSATB1/K562 cells, respectively (Fig. S1 A–D). The expression of the exogenous wild-type or NMTS-deficient SATB1 was confirmed with RT-PCR analysis (Fig. S1E).

Wild-type but not NMTS-deficient SATB1 over-expression has regulatory effects on β-like globin genes expression

K562 cells express predominantly ε- and γ-globin, and trace level of β-globin mRNA (Fig. S2). RT-PCR analysis indicated that, in SATB1/K562 cells, the changes of ε-, γ-, and β-globin transcripts levels were in consistent with previous report [11]. On the contrary, in mSATB1/K562 cells, the mRNA levels of these genes were close to those in the mock and untransfected K562 cells (Fig. S2). These results suggested that NMTS-deficient SATB1 has no regulatory effects on β-like globin genes expression as wild-type SATB1 has.

Both wild-type and NMTS-deficient SATB1 induce looping of the β-globin locus

It is reported that activated β-globin locus prefers to extrude from its CT [4]. Firstly, to confirm the relationship between moving out and activation of β-globin locus, we applied FISH to observe the positioning of β-globin cluster relative to its CT in either the uninduced K562 cells or hemin induced K562 cells. The β-globin locus did not show significant relocation (only 13.8%) away from its CT in uninduced K562 cells (Fig. 1A and F); while in hemin induced K562 cells, the percentage increased to 37% (Fig. 1B and F). This result confirmed that the extruding of β-globin locus is in association with its activation.

Next, we performed FISH to determine the effects of SATB1 on β-globin cluster relocation. About 30% β-globin alleles located outside of the CT No.11 in SATB1/K562 cells (Fig. 1C and F). This result implied that SATB1 may play roles in relocating β-globin locus away from its CT. Unexpectedly, in mSATB1/K562 cells, although NMTS-deficient SATB1 had no effects on β-like globin genes expression, the percentage of relocated β-globin locus (32%) had no significant difference from that in SATB1/K562 cells (Fig. 1D and F). The relocation was not induced by the vector itself as the frequency of looping in the EGFP/K562 cells (12%) was very similar to that in the uninduced K562 cells (Fig. 1E and F). These data demonstrated that both wild-type and NMTS-deficient SATB1 induce looping of the β-globin locus.

Wild-type not NMTS-deficient SATB1 anchors β-globin cluster on nuclear matrix

To distinguish the extrusion of β-globin locus induced by wild-type and NMTS-deficient SATB1, nuclear halos were prepared from K562, SATB1/K562 and mSATB1/K562 cells for FISH assays with BAC probes covering β-globin locus. The percentage of nuclear matrix associated β-globin clusters in SATB1/K562 cells (95%, Fig. 2B) is similar to that in K562 cells (93%, Fig. 2A). In contrast, in mSATB1/K562 cells, the percentage is only 71% (Fig. 2C). As the NMTS-deficient SATB1 lost part of the nuclear matrix binding character, these results suggested that NMTS was involved in the function as anchors.

SATB1 affects binding statuses of Pol II and GATA1 in a matrix dependent manner

To further characterize the SATB1-associated nuclear relocation of β-globin locus, we detected the binding patterns of Pol II and GATA1 on the pivot *cis*-elements within β-globin locus in K562, SATB1/K562 and mSATB1/K562 cell lines via ChIP assays. As necdin is silent in the erythroid cell lines, the binding situations of these factors on necdin promoter were used as negative control.

Our results showed that the binding frequencies of Pol II increased on HS2 and ε-gene promoter but decreased on γ-globin gene promoter in SATB1/K562 cells compared to K562 cells. While there exhibited no significant differences between mSATB1/K562 cells and K562 cells of Pol II binding status on these detected sites (Fig. 3A). These properties were consistent with the changes at transcriptional levels of β-like globin genes.

GATA1 is a repressor of ε-globin gene [18]. Since no significant change of GATA1 expression level was found when wild-type SATB1 was over-expressed in previous study [11], we further examined binding statuses of GATA1 on three reported binding sites within the 5′ flanking region of ε- globin gene (+3, −165, −213) [19]. It demonstrated that the binding frequencies of GATA1 on all these three sites were decreased in SATB1/K562 cells and were similar in mSATB1/K562 cells compared to K562 cells (Fig. 3B).

The differences between the binding patterns of the Pol II and GATA1 on β-globin locus in SATB1/K562 and mSATB1/K562 cells implied that SATB1 affects binding statuses of them in a matrix dependent manner.

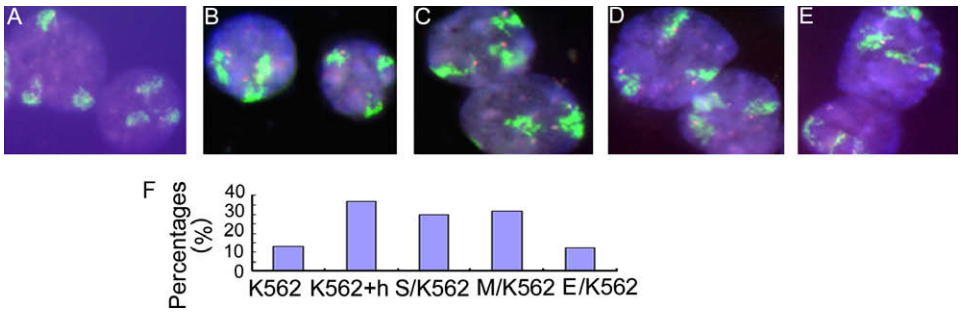

Fig. 1. The β-globin cluster was induced to protrude from CT No. 11. (A–E) FISH results showed the nuclear location of β-globin cluster with respect to CT No. 11 in K562 cells (A), K562 cells induced by hemin (B), SATB1/K562 cells (C), mSATB1/K562 cells (D) and EGFP/K562 cells (E), respectively. The β-globin locus are detected with a Texas red-conjugated probe (red spots), and the CT No. 11 are detected with a FITC-conjugated probe (green). As K562 cells are pseudotriploid with three No. 11 chromosomes, there are three red signals in each cell. BAC signals were considered looped when found outside their painted CTs without touching their borders, while signals were considered unlooped when found in the interior or on the surfaces of CTs. (F) The percentages of the extruded β-globin cluster in all these cell lines. At least 50 and up to 80 nuclei were scored. The frequencies from K562 and SATB1/K562 cells, K562 and mSATB1/K562 cells were both significantly different ($P < 0.05$).

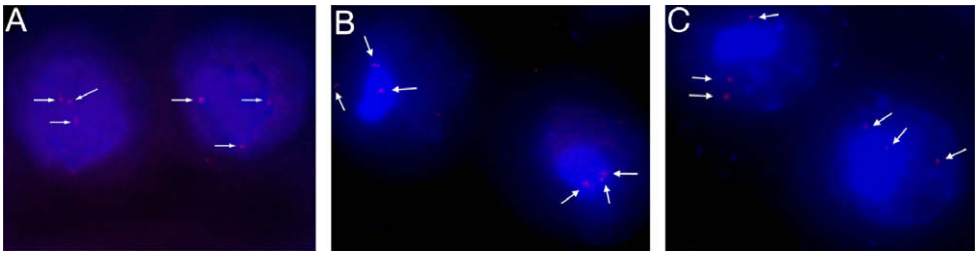

Fig. 2. The location of β-globin cluster relative to the nuclear matrix. (A–C) The location of β-globin cluster relative to the nuclear matrix in K562 (A), SATB1/K562 (B) and mSATB1/K562 cells (C), respectively. The β-globin locus is detected with a Texas red-conjugated probe (red spots). As K562 cells are pseudotriploid with three No. 11 chromosomes, there are three red signals in each cell pointed by white arrows in each cell. The nuclei were stained with DAPI. The light blue represented the looped DNA that was not associated with matrix, whereas the dark blue represented the nuclear matrix where the DNA anchored. At least 45 and up to 60 nuclei were scored. Significant difference was found between the frequencies from SATB1/K562 and mSATB1/K562 cells ($P < 0.05$).

Chromatin modifications are differentially regulated by wild-type and NMTS-deficient SATB1

To determine if the relocation of β-globin cluster induced by wild-type or NMTS-deficient SATB1 was coupled with epigenetic changes, acetylation status of core histones at HS2, ε-, γ- and β-globin promoters were monitored in HeLa, K562, SATB1/K562 and mSATB1/K562 cells with ChIP assays. The histone modification state at GAPDH gene promoter was used as endogenous control.

We took the chromatin modification level on β-globin cluster in HeLa cells as base line because the β-like globin genes are silent and the cluster is relatively hypoacetylated. In K562 cells, H3 acetylation level increased by 2-fold at the ε-and γ-globin gene promoters, and showed more moderate increase at HS2 (1.4-fold) and β-globin gene promoter (1.3-fold); H4 acetylation levels through the locus are mildly higher (1.4–1.7-fold). Such modification states are consistent with the previous results that the embryonic and fetal β-like globin genes are relatively more active. In SATB1/K562 cells, H3 acetylation increased by 4.6-fold at the ε-globin promoter, and about 2-fold increase was observed at HS2, γ- and β-globin promoters; the cluster displayed homogeneous degree of elevation of H4 acetylation by 2.4–3.1-fold throughout the sequences (Fig. 4C). The changes of chromatin modification on β-globin cluster observed in SATB1/K562 cells elucidated that over-expression of SATB1 activated the cluster, especially the ε-globin gene. However, in mSATB1/K562 cells, H3 acetylation level increased at HS2 and β-globin promoter by 1.5 and 1.8-fold, respectively, with comparable more elevation at ε- (2.2-fold) and γ-globin (2.4-fold) promoters; H4 acetylation levels were slightly higher throughout the β-globin cluster (1.5–1.8-fold) (Fig. 4D), the result was different from that observed in SATB1/K562 cells but similar to that in K562 cell and noticeably, the H3 hyperacetylation peak at ε-globin promoter vanished.

Discussion

Looping away from CTs has emerged as a prominent feature of multigene loci and gene-dense chromosome domains. It is believed that looping may be the movement of decondensed chromatin away from the more densely packaged chromatin of a given chromosome [2,3]. It is also presumed that looping a gene (or gene array) away from the CT would bring it into the proximity of nuclear bodies positioned in the interchromatin and thereby facilitate transcription [8]. However, the correlation between looping and transcriptional activation is still unclear. Here, we tackled the question by investigating the regulatory roles of SATB1 in the looping process and transcription activity of human β-globin locus.

Over-expression of either wild-type or the NMTS-deficient SATB1 could induce the protrusion of β-globin cluster from its CT. It has been reported that abundant SATB1 proteins, either endogenous or exogenous, promoted associated protein to co-distribute in the same subnuclear compartment [6,8,10]. NMTS-deficient SATB1, though fails to form the unique birdcage-like network, also induces relocation of combined proteins [10]. Therefore, β-globin cluster binding with SATB1 may be also induced to relocate away from its CT and co-distribute in the interchromatin space with SATB1 during the formation of SATB1 multimers, either birdcage-like or vacuolar-like.

The protrusion of β-globin locus in SATB1/K562 cells was accompanied by the reciprocal changes of ε- and γ-globin gene

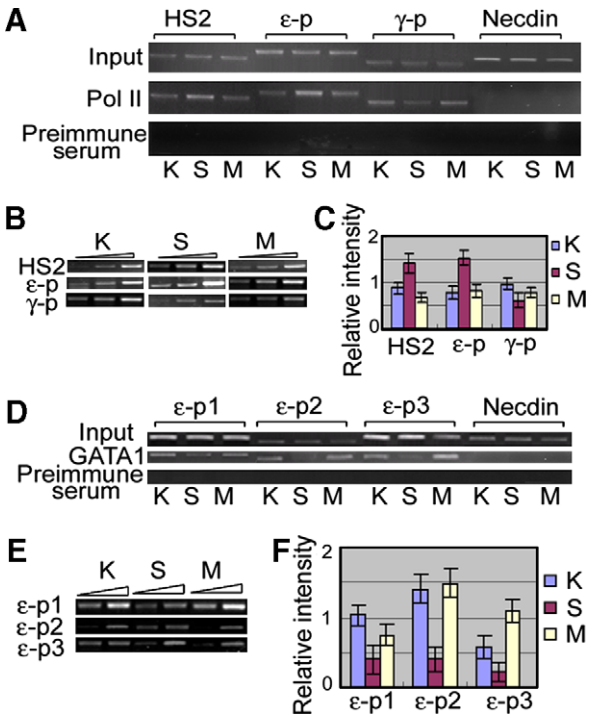

Fig. 3. Binding situations of Pol II (A–C) and GATA1 (D–F) on β–globin cluster. (A) ChIP assays were performed to detect the Pol II binding situations on HS2, ε- and γ-promoter of the β-globin cluster in K562 (K), SATB1/K562 (S) and mSATB1/K562 (M) cells. Necdin was used as a negative control. (D) ChIP assays were performed to detect the GATA1 binding situations on HS2 and upstream regions of ε-promoter of the β-globin cluster in K562 (K), SATB1/K562 (S) and mSATB1/K562 (M) cells. (B and E) To obtain the PCR products in a linear range, input from the three cell lines were amplified with different cycle numbers, which were 28, 33 and 36 in B and 30 and 36 in E, respectively. (C and F) Relative intensity of each sample at each site was equal to bound/input proportion.

expressions, while in mSATB1/K562 cells, there had little effects on the β-like globin genes expression. The results of halo preparation combined with FISH analysis indicated that the looping out in these two conditions are actually different. The percentage of nuclear matrix associated β-globin clusters was much higher in SATB1/K562 cells than that in mSATB1/K562 cells. The interchromatin region has been supposed to be functionally equivalent to a dynamic *in situ* nuclear matrix [20]. Our results supplied evidence with discrepancy: β-globin cluster repositioned in the interchromatin space is not necessarily associated with nuclear matrix; on the other hand, though mostly positioned in the CT, 93% β-globin clusters were found associated with nuclear matrix in K562 cells. We thus suppose that both looping out of the CT and association with nuclear matrix mediated by SATB1 are prerequisites of β-globin cluster activation.

It was reported previously that NMTS is a key player in SATB1-related regulation [9,10]. Our data, however, showed that there were still matrix positioned β-globin clusters in mSATB1/K562 cells. Part of them may be due to the function of endogenous wild-type SATB1; another possibility is that SATB1 has more than one domain that specifies matrix binding. The presence of multiple NMTSs has been observed in other proteins, such as steroid hormone receptors [21].

It was proposed that the patterns of H3 and H4 acetylation are generally consistent and mark the open chromatin structure [22]. In contrast to the homogeneous pattern of H4 acetylation observed throughout β-globin locus, there are H3 hyperacetylation peaks near the promoters representing the activation of specific genes [22]. Our results indicated that besides the matrix-associated looping of β-globin locus into the interchromatin space, over-expression of wild-type SATB1 was also coupled with increased H3 and H4 acetylation levels throughout the locus, with H3 hyperacetylation peak at ε-globin gene promoter. Accordingly, this nuclear relocation of β-globin cluster was concomitant with establishment of an open chromatin configuration and activation of ε-gene promoter. Furthermore, our data revealed increased binding of Pol II at HS2 and ε-gene promoter and decreased binding of GATA1 in the upstream region of ε-gene promoter. This might be consequences of the chromatin remodeling and the recruitment of transacting factors by SATB1. These factors could modify the chromatin further or regulate the promoter activity directly.

In mSATB1/K562 cells, similar to the untransfected K562 cells, H3 and H4 acetylation levels were moderately higher than that in HeLa cells. Though H3 acetylation levels slightly increased near ε- and γ-globin gene promoters, there was no obvious H3 hyperacetylation peak on the β-globin cluster. Although it was assumed that looping itself is a decondensing process [23], our data didn't show an effective opening of chromatin structure caused by the NMTS-deficient SATB1-induced looping process. Combined with the analysis on binding status of transacting factors and the expression levels of β-like globin genes, these results suggested that SATB1 regulates the multi-step activation of β-like globin genes in a matrix dependent manner.

In conclusion, our results combined with previous studies indicated that over-expression of SATB1 in K562 cells induced the looping out of β-globin cluster from its CT and associated with the nuclear matrix. During this process, open chromatin was established throughout the whole locus with specialized H3

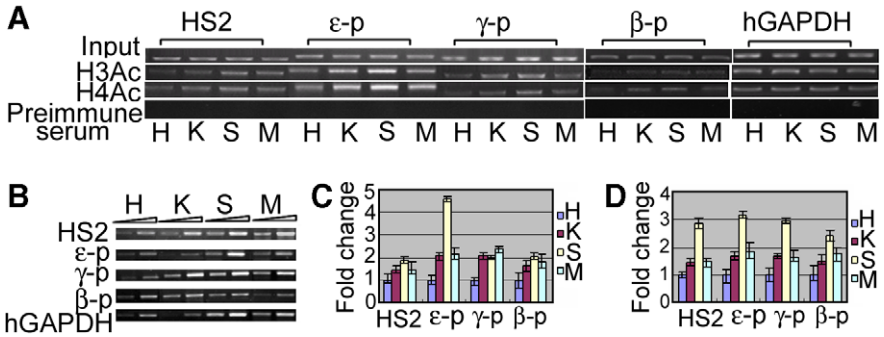

Fig. 4. Chromatin modifications of β-globin cluster. (A) ChIP assays were performed to detect the acetylation levels of H3 and H4 at HS2 and the promoters of β-like globin genes in HeLa (H), K562 (K), SATB1/K562 (S) and mSATB1/K562 (M) cells. (B) To obtain the PCR products in a linear range, input from the four cell lines were amplified with different cycle numbers, which were 30 and 36, respectively. (C and D) Relative intensity of H3 (C) or H4 (D) acetylation at one site was equal to "[Histone modification (X)/Input (X)]/[Histone modification (hGAPDH)/Input (hGAPDH)]", and then the relative intensities from K562, SATB1/K562 and mSATB1/K562 cells were compared to that from HeLa cells to get the fold changes.

hyperacetylation peak at ε-globin gene promoter. Together with the binding of important transacting factors, ε-globin gene expression was promoted. Our data provided evidence that SATB1 regulates β-globin cluster through linking nuclear architecture, chromatin structure and functional organization of DNA sequences. Furthermore, analysis on K562 cells over-expressing NMTS-deficient SATB1 elucidated that the regulatory roles of SATB1 are dependent on its association with nuclear matrix.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bbrc.2009.03.122.

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