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SATB1 regulates SPARC expression in K562 cell line through binding to a specific sequence in the third intron

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Abstract

Special AT-rich binding protein 1 (SATB1), a cell type-specific nuclear matrix attachment region (MAR) DNA-binding protein, tethers to a specific DNA sequence and regulates gene expression through chromatin remodeling and HDAC (histone deacetylase complex) recruitment. In this study, a SATB1 eukaryotic expression plasmid was transfected into the human erythroleukemia K562 cell line and individual clones that stably over-expressed the SATB1 protein were isolated. Microarray analysis revealed that hundreds of genes were either up- or down-regulated in the SATB1 over-expressing K562 cell lines. One of these was the extra-cellular matrix glycoprotein, SPARC (human secreted protein acidic and rich in cysteine). siRNA knock-down of SATB1 also reduced SPARC expression, which was consistent with elevated SPARC levels in the SATB1 over-expressing cell line. Bioinformatics software Mat-inspector showed that a 17 bp DNA sequence in the third intron of SPARC possessed a high potential for SATB1 binding; a finding confirmed by Chromatin immunoprecipitation (ChIP) with anti-SATB1 antibody. Our results show for the first time that forced-expression of SATB1 in K562 cells triggers SPARC up-regulation by binding to a 17 bp DNA sequence in the third intron.

Keywords: Nuclear matrix attachment region (MAR); SATB1; SPARC; Intronic MAR; Gene regulation

Special AT-rich binding protein 1 (SATB1) is a cell type-specific nuclear matrix attachment region (MAR) DNA-binding protein that is predominantly expressed in thymocytes and pre-B cells. SATB1 recognizes a specialized sequence rich in both As and Ts, but either Cs or Gs on one strand [1]. This protein contains a dimerization domain that shares similarity with the PDZ motif, identified as an indispensable element for interaction with MAR sequences [2]. As a nuclear matrix protein, SATB1 has a unique cage-like distribution that selectively tethers it to a specific DNA sequence in its ''network'', and regulates gene expression by recruiting HDAC1 (histone deacetylation complex 1) to these specific DNA sequences over a long distance [3,4]. Thus, SATB1 is a transcriptional regulator that has the ability to participate in several biological processes [5,6].

Secreted protein acidic and rich in cysteine (SPARC; also termed osteonectin and BM-40) is a Ca^{2+}-binding glycoprotein in the matricellular group of proteins located on chromosome 5, which were initially identified in bone, but are distributed widely through many other tissues and cell types [7]. SPARC has numerous effects on cell shape, proliferation, adhesion, and tissue response injury through both direct and indirect interactions with growth factors and extra-cellular matrix (ECM) proteins [8,9]. SPARC also interacts with platelet-derived growth factor and vascular endothelial growth factor (VEGF), and abrogates their binding to cognate receptors. Helene et al. demonstrated that matrix metalloproteinase (MMP)-3 digests SPARC into three major fragments that function to bind Cu^{2+}, bind Ca^{2+}, and inhibit cell proliferation, respectively [6]. The mechanism by which SPARC inhibits proliferation

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is not completely understood. It is suggested that SPARC interacts with cell-surface receptors to activate downstream signaling factors, a process dependent, at least in part on heterotrimeric G-protein coupled signaling [9]. Thus, SPARC is not only a modulator of cellular and extra-cellular matrix interactions, but also a regulator of signal transduction, matrix remodeling, and cell proliferation.

In this report, we showed by microarray analysis that over-expression of SATB1 in K562 cells induced aberrant expression of numerous genes. In addition, a slow rate of proliferation was observed in SATB1 over-expressing K562 cells by MTT assay. One of the aberrant genes, SPARC, was significantly up-regulated in SATB1 expressing cells, and siRNA knock-down of SATB1 simultaneously reduced SPARC expression. We further showed by ChIP analysis that SATB1 interacts with a 17 bp sequence in the third intron of SPARC, providing new evidence that SATB1 is a regulator of SPARC.

Materials and methods

Cell culture and transfection. The human erythroleukemia cell line, K-562 (ATCC: CCL-243), was obtained from the American Type Culture Collection (Manassas, VA). K-562 cells were cultured in PRIM 1640 containing 10% fetal calf serum, penicillin (100 μ/ml), and streptomycin (100 μg/ml) at 37 °C in a humidified atmosphere with 5% CO_2. The cells were seeded in a six well-plate at a density of 4×10^5, and transfection was performed with lipofectamine 2000 (Invitrogen) according to the manufacturer's instructions. Antibiotic-resistant cells were selected using 800 μg/ml geneticin (G418) and an individual cell line clone was obtained after four weeks and maintained with 200 μg/ml geneticin.

RT-PCR and Western blot analysis. Total RNA was isolated and first-strand cDNA was synthesized using M-MLV reverse transcriptase (RT) and oliog-d(T) (Invitrogen). The cDNA was used to amplify SATB1 and β-actin served as a control. The primer sequences of SATB1 and β-actin were as follows: SATB1 forward: CATTCAAGCTCCTTTCCCTTTC, SATB1 reverse: TGGGCTCGTATCAACACCTATC; β-actin forward: CCAAGGCCAACCGCGAGAAGATGAC, β-actin reverse: AGGGTACATGGTGGTGCCGCCAGAC. Following amplification, 10 μl of the PCR products were separated on a 1.5% agarose gel and visualized by ethidium bromide staining. For Western blotting, 40 μg of total protein was separated by 10% sodium dodecyl sulfate (SDS)–polyacrylamide gel electrophoresis. The gel was transferred to a nitrocellulose membrane and blocked with TBST (10 mM Tris, pH 8.0, 150 nM Nacl, and 0.05% Tween 20) and 5% nonfat milk for 1 h at room temperature. Blots were incubated overnight at 4 °C with anti-SATB1 polyclonal antibody (BD Bioscience) or anti-SPARC polyclonal antibody (Santa Cruz), washed with TBST, and incubated with HRP-conjugated secondary antibody for 1 h at room temperature. Visualization of bound antibody was performed using the Super Signal West Pico Trial Kit (Pierce).

Cell proliferation assay. Cells were seeded in 96-well plates at a density of 5×10^3 per well and incubated for 48 h in the absence of fetal bovine serum. 20 μl MTT ([3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] at 5 mg ml^{-1} (Sigma, USA) was added to each well to make a final concentration of 5 μg/ml and incubated for 4 h in a CO_2 incubator. Media was removed and replaced with 150 μl DMSO (Sigma, USA), incubated for 5 min at 37 °C, transferred to a microplate reader, and measured at 570 nm wavelength. Measurements were repeated every 24 h for seven days. Each group contained three repeat wells.

Microarray and real-time PCR confirmation. Five micrograms RNA from the K562 and K562-SATB1 cells was labeled using the Agilent Fluorescent LinearAmplification kit (Palo Alto, CA). Labeled RNA was further purified using the Qiagen RNeasyMini kit protocol for liquid samples (Valencia, CA). Two pairs of labeled cRNA were prepared from four independent RNA extractions, hybridized to the Agilent Human 1A Oligo Array, and washed using the Agilent Insitu Hybridization Kit Plus. cRNA was labeled with Cy5 and Cy3 for ''swapped''-labeling co-hybridizations. Microarrays were scanned using an Agilent DNA Microarray Scanner and expression data were obtained using Agilent Feature Extraction software (version 6.1.1), by setting the parameters on default. Results were confirmed using real-time PCR. The real-time PCR primers used were as follows: SATB1 forward: GTGGGTACGCGATG AACTGA, SATB1 reverse: TGTTAAAAGCCAGTGCAA; SPARC forward: TCACATTAGGCTGTTGGTTCAAA, SPARC reverse: CGCTGACCACTTCCCAGAGA; β-actin forward: CCTGGCACCCA GCACAAT, β-actin reverse: GCCGATCCACACGGAGTACT.

RNA interference. K562-SATB1 cells were seeded in a six well-plate at a density of 4×10^5/well. Two hundred nanomolars SATB1-specific small interfering RNAs (siRNA) (Dharmacon, SMART poll siRNA) or a non-targeting siRNA (Dharmacon, siCONTROL Non-Targeting siRNA #1) were transfected into the cells using lipoectamine 2000 (Invitrogen), according to manufacturer's instructions. Cells were incubated for 60 h in RPMI 1640 medium containing 2% fetal bovine serum and RNA and protein extracts were prepared for real-time PCR and Western blotting.

Mat-inspector software analysis and ChIP. The whole 26,706 bp SPARC gene sequence was analyzed using Mat-inspector (http://www.genomatix.de/online_help/help_matinspector/matinspector_help.html), a transcription-factor analysis software provided online by Genomatix Software GmbH. Crosslinked chromatin was prepared from K562 and K562-SATB1 cells, and 4×10^7cells were fixed with 1% formaldehyde and incubated for 3 min at 37 °C. Chromatin was washed in cold PBS, resuspended, incubated on ice for >10 min, and sonicated 3× for 10 s each with 220 V (JT92-II, Ning Bo Xinzhi tech institute), using 30 s intervals (conditions were established from a preliminary test in order to achieve sonicated DNA sequences with a size ranging from 500 to 1500 bp). For ChIP analysis, the sample was pre-cleared with preimmune salmon sperm DNA/protein agarose for 30 min at 4 °C, and specific antibodies against SATB1 and non-specific IgG (Santa Cruz) were added individually and rotation incubated overnight at 4 °C. Bound and input chromatin samples were placed in 0.5% (wt/vol) SDS and incubated at 65 °C for 4 h to reverse the formaldehyde cross-linking. DNA was further purified by phenol–chloroform extraction, and ethanol precipitated using 10 μg glycogen as a carrier. Purified DNA was amplified by PCR using specific primers located in the third intron of the 17 bp potential binding site. The primers used were as follows: forward: TCCTACTCCAAGTTGAAATG and reverse: TAG GAAAATTGACATCCAGAG. PCR conditions included 1 cycle of 95 °C for 5 min, and 35 cycles of 94 °C for 40 s, 58 °C for 40 s, and 72 °C for 40. The 120 bp long PCR products were analyzed by 2.5% agarose gels electrophoresis. Quantitative real-time PCR was performed to compare the disparity of binding between STAB 1 and the 17 bp binding sequence in SATB1 transfected and untransfected K562 cells.

Statistical analysis. Statistical analysis was carried out using standard methods. Error bars show the SD of the mean.

Results

Over-expressing SATB1 in the human K562 cell line

To investigate the influence of SATB1 on global gene regulation in the K562 cell line, a SATB1 expression vector was transfected into K562 cells, which have low endogenous expression of SATB1, allowing us to attribute any unusual effects observed in K562-SATB1 cells to the newly introduced SATB1. Following a three week G418 selection (800 μg/ml), we were able to isolate positive clones that stably over-expressed SATB1 and use these for analysis. RT-PCR and Western blotting confirmed the SATB1 expression disparity between K562-SATB1 and normal K562 cells (Fig. 1A and B),

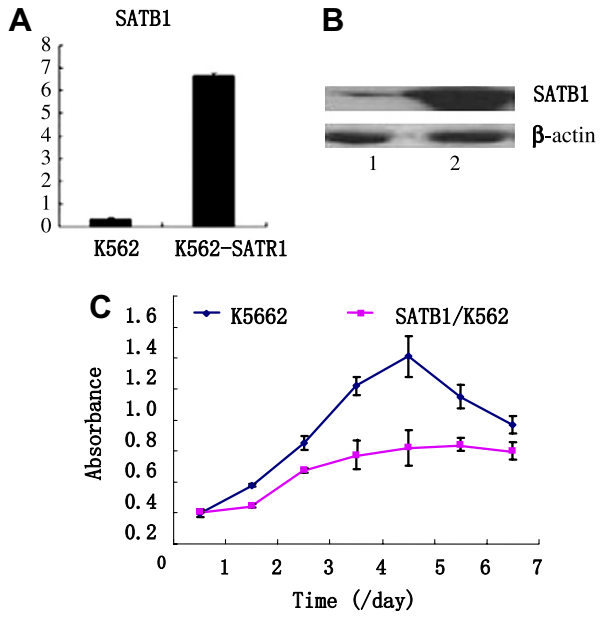

Fig. 1. Stable over-expression of SATB1 in the K562 cell line. (A) The level of SATB1 transcripts differs between K562 cells (lane 1) and over-expressed K562-SATB1 cells (lane 2) by real-time PCR, using β-actin as a positive control. (B) Western blot of K562 cells (lane 1) and over-expressed K562-SATB1 cells (lane 2) using anti-SATB1 antibody and β-actin as a loading control. (C) The K562 and over-expressed K562-SATB1 cells were seeded in 96-well plates at a density of 5×10^3 per well. Each well was stained with 20 μl sterile MTT (Sigma, USA) for 4 h at 37 °C, replaced with 150 μl DMSO (Sigma, USA), and mixed for 10 min. Spectrometric absorbance at 570 nm wavelengths was measured on a microplate reader. Each group contained four wells and was repeated three times.

indicating that SATB1 expression was 10× higher in K562-SATB1 than K562 cells. K562-SATB1 cell proliferation was significantly slower than normal K562 cell proliferation over seven days, as shown using the MTT assay (Fig. 1C). We assumed that this was due to SATB1 over-expression.

Microarray analysis of global gene expression in K562-SATB1 cells

To study the disparity in global gene expression between K562-SATB1 and normal K562 cells, we carried out microarray analysis. Two individual clones of the K562-SATB1 cell line were analyzed and genes that were up- or down-regulated on both CHIPs were assessed. We found 59 up-regulated and 75 down-regulated genes in the K562-SATB1 cells that were not observed in the K562 cells. Partial genes that have special biological functions are listed in Table 1 (Fig. 2).

RNA interference

While microarray and Western blot both demonstrated that SATB1 over-expression up-regulates SPARC, it was important to illustrate that SATB1 down-regulation could inhibit SPARC. We transfected SATB1-specific siRNA into K562-SATB1 and K562 and extracted RNA and protein for real-time PCR and Western blot analyses. Both analyses showed that the SATB1 specific siRNA-induced a decrease in SATB1 expression that was accompanied by a significant decrease in SAPRC (Fig. 3).

Interaction between SATB1 and SPARC

To identify whether the expression increase of SPARC was the result of SATB1over-expression, we analyzed the SPARC gene sequence using the transcription factors analysis software, Mat-inspector (http://www.genomatix.de/online_help/help_matinspector/matinspector_help.html) to identify whether specific sites are required for direct interactions between SATB1 and SPARC (Table 2). A 17 bp sequence localized in the third intron of SPARC displayed strong SATB1 binding ability. The ChIP assay was applied

Table 1
Genes expressed aberrantly in K562-SATB1 as compared to K562 cells

Gene symbol	GenBank	Fold change	Function
SATB1	NM_002971	6.3	Involved in necrosis and may be involved in T-cell specific chromatin organization and developmental processes
SPARC	NM_003118	4.7	Plays a regulatory role in cell proliferation, morphogenesis, and tissues responses to injury, stimulates angiogenesis, may initiate bone mineralization
IGFBP2	NM_000597	4.7	Plays a regulatory role in cell proliferation, morphogenesis, and tissues responses to injury, stimulates angiogenesis, may initiate bone mineralization
TAF11	NM_005643	3.7	Interacts with TAF2F, TAF2D, and viral transcription factors, acts as a transcriptional coactivator for several nuclear receptors
CDW52	NM_001237	2.91	A GPI-anchored protein involved in the activation of T cells, monocytes, and granulocytes, mediated cell lysis and as a therapeutic target for several immune system-mediated diseases
L23A	NM_016584	−5.4	Stimulates proliferation of memory and naive T cells, linked to STAT signaling
AREG	NM_001657	−4.2	Epidermal growth factor receptor (EGFR) ligand, induces proliferation of epithelial cells and psoriatic lesions
HSPA6	NM_002155	−3.1	Heat shock 70 kDa protein 6 (HSP70B), a member of the HSP70 family of molecular chaperones, acts in response to heat shock, up-regulated during Fas (TNFRSF6)-mediated apoptosis
MYB	NM_005375	−2.3	A cell cycle regulator and transcription factor that stimulates cellular proliferation and inhibits apoptosis, functions in hematopoiesis; gene amplification is associated with leukemias

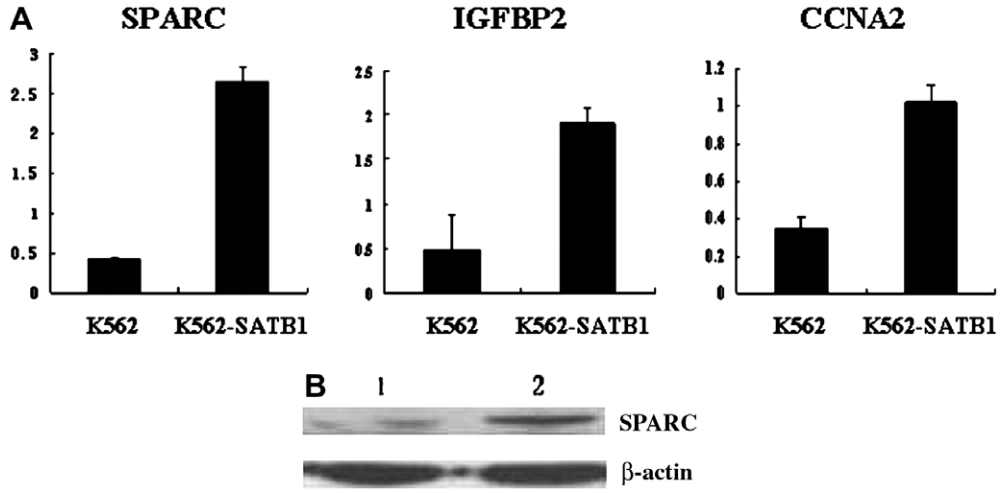

Fig. 2. (A) Confirmation of SPARC, IGFBP2, and CCNA2 transcripts level between K562 and K562-SATB1 cells using quantitative real-time PCR. (B) Western blot of SPARC in K562 (lane 1) and K562-SATB1 cells (lane 2) using donkey SPARC specific antibody (Santa Cruz) and β-actin as a loading control.

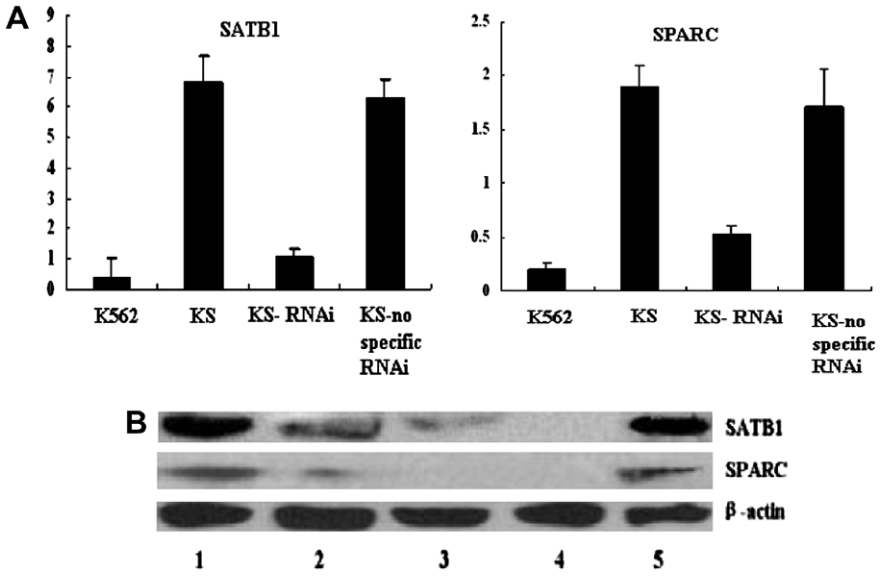

Fig. 3. (A) Real-time PCR analysis of SATB1 and SPARC expression after transfection with SATB1-specific siRNA (KS represents the K562-SATB1 cell line). (B) K562-SATB1 cells were transfected with SATB1-specific siRNAs, and incubated for 60 h prior to protein extraction and preparation. Western blots were incubated with SATB1-spcific monoclonal antibodies (BD) or SPARC specific monoclonal antibodies (Santa Cruz), and β-actin was used as a loading control. Lane 1: K562-SATB1 cells, lane 2: K562 cells, lane 3: K562-SATB1 cells transfected with SATB1 siRNA, lane 4: K562 cells transfected with SATB1 siRNA, lane 5: K562-SATB1 cells transfected with non-specific siRNA.

Table 2
SPARC full sequence analysis using Mat-inspector shows the potential SATB1 binding sequence within the SPARC gene

Transcription factor	Description	Binding sequence
V$CART/ XVENT2.01	*Xenopus* homoedomain factor Xvent-2; early BMP signaling response	cc*TAAT*aatact*acta*a
V$SATB/SATB1.01	Special AT-rich sequence-binding protein 1; predominantly expressed in thymocytes, binds to matrix attachment regions (MARs)	taatactac*TAAT*aata
V$BRNF/BRN3.02	Brn-3, POU-IV protein class	atactacT*AAT*aatatcac
V$OCT1/OCT1.05	Ocatmer-binding factor 1	aAT*AT*cac*ac*tgtga
V$EV11/MEL1.03	MEL1(MDS1/EVI 1-like gene 1) DNA-binding domain 2	actatagag*aa*a*GAT*Gatga

Note: the letters in italized represent hypothetic core base of MAR sequence.

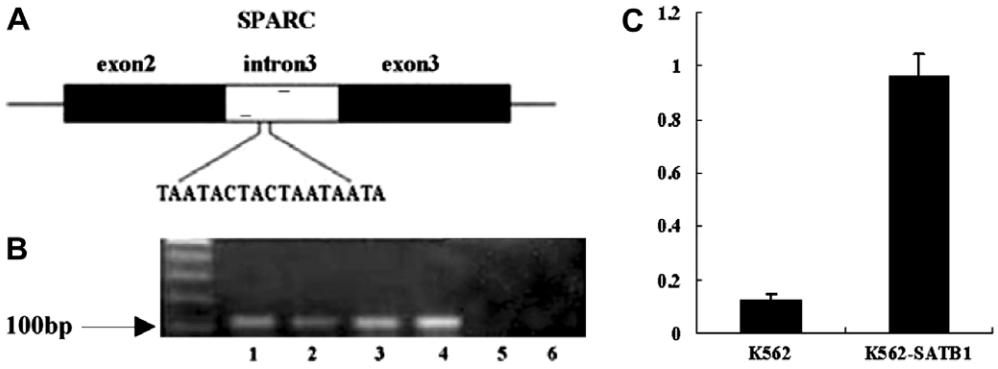

Fig. 4. (A) A potential DNA sequence that binds SATB1 in the third intron of SPARC, where two strigulas represent locations of the forward and reverse primers for ChIP PCR analysis. (B) ChIP DNA selected using the anti-SATB1 antibody was amplified with specific primers. Lanes 1 and 3 represent K562 and SATBl-K562 cells as a positive control, lanes 2 and 4 represent ChIP DNA obtained from K562 and SATBl-K562 cells, lane 5 represents non-specific IgG, lane 6 represents non-specific primer. (C) ChIP DNA from K562 and SATBl-K562 cells were subjected to quantitative real-time PCR analysis. SATB1 selected ChIP DNA was diluted to Ing.

to verify the authenticity of binding between this 17 bp DNA sequence and SATB1. We designed specific primers to amplify a 120 bp DNA fragment of the SPARC gene that contains this 17 bp sequence, and selected inputs of K562 and K562-SATB1 as positive controls. Non-specific IgG was used as a negative control and non-specific primers for GAPDH were used for PCR amplification, using purified DNA as the templates. Direct binding between STAB1 and the 17 bp sequence in both K562-SATB1 and K562 cells was shown by 2.5% agarose gel electrophoresis. However, quantitative real-time PCR demonstrated increased binding in K562-SATB1 than K562 cells (Fig. 4).

Discussion

SATB1-K562 cell proliferation was significantly lower than K562 cell proliferation over a seven-day period. This anti-proliferation effect is likely due to the cooperation of several genes rather than being limited to two or three factors that are directly related to the target [10]. Thus, we applied Angilient human cDNA Gene Microarray analysis to explore differences gene expression between K562 and K562-SATB1 cells. Fifty-nine genes were up-regulated and 75 genes were down-regulated in K562-SATB1 cells. We classified these into several categories and found that histone or histone related proteins represented the highest percentage of up-regulated proteins, a result that confirmed the close relationship between SATB1 and the formation of chromatin structure [3]. In addition, we found that 8% of the up-regulated gene and 12% of down-regulated genes function as regulators of proliferation and apoptosis (data not shown). This correlates with our MTT result that the proliferative capacity of K562-SATB1 cells is lower than normal K562 cells, even though the mechanism remains unknown.

There is growing evidences that gene transcription activity is influenced by nuclear organization [11]. Open chromatin structure formation and histone acetylation are closely related to gene activation while histone methylation has a role in gene inactivation. SATB1 functions as a nuclear matrix binding protein that forms a unique cage-like structure in thymocytes that tethers the specific DNA sequence to its network [12], and facilitates formation of an open chromatin structure and participates in genes regulation. Alcarez et al. show that SATB1 knockout mice only live for three weeks after birth as a result of the aberrant expression of hundreds of genes (at least 2% of total genes, either expressed or silent) [13]. We found that the extra-cellular matrix protein, SPARC, was significantly higher in the K562-SATB1 than K562 control cell lines for the first time. The SATB1 knockdown by RNAi mediated decreased SPARC expression and reinforced our speculation that SATB1 over-expression induces up-regulation of SPARC. Furthermore, application of the transcription factor analysis software, Mat-inspector (http://www.genomatix.de/online_help/help_matinspector/matinspector_help.html), identified a 17 bp sequence in the third intron of SPARC that displayed a strong tendency to bind SATB1. Thus, we designed specific primers for PCR analysis of chromatin fragments that were immunoprecipitated with the anti-SATB1 antibody, in order to verify the authenticity of this 17 bp sequence. These results confirmed our hypothesis that SATB1 directly binds to the 17 bp sequence in the third intron of SPARC *in vivo*, and quantitative real-time PCR further demonstrated that binding was higher in K562-SATB1 than K562 cells. Importantly, the 17 bp sequence is full of both As and Ts but either Cs or Gs, which matches the features of a SATB1 binding sequence. While it is known that SATB1 preferentially binds to MAR sequences or DNase I HS sites (DNase I hypersensitive sites) [14], the 17 bp sequence of SPARC has not been defined as a MAR or DNase I HS site in previous reports. Thus, identification of this sequence remains unknown.

The matrix glycoprotein, SPARC is already shown to inhibit adhesion and proliferation. However, the inhibition of cell proliferation results from the cooperation of multiple factors. We found several genes that regulate proliferation, in addition to SPARC, that were aberrantly expressed in K562-SATB1 cells. The α-subunit, p19, of interleukin 23, which stimulates proliferation of memory and naive T cells, underwent a 3× decrease [15], and amphiregulin (schwannoma-derived growth factor), an epidermal growth factor receptor (EGFR) ligand that induces epithelial cell proliferation and psoriatic lesions underwent a 4× decrease [16]. While all these factors are responsible for inhibiting cell proliferation, SATB1 likely plays a primary role. In addition to inhibiting adhesion and proliferation, SPARC is also correlated with the progression and angiogenesis of cancer [17]. There are also proofs demonstrated that the expression of SPARC is closely related with patient mortality of bladder cancer, however the mechanism is not completely elucidated. It is well known that SPARC expression is significantly correlated with matrix metalloproteinase-2 expression [18], and Miyake et al. also found that over-expression of insulin-like growth factor binding protein (IGFBP2) increase the production of matrix metalopeptidase 2 (MMP-2), and enhance the metastatic potential of certain bladder cancers [19]. Since, our microarray results show that both IGFBP2 and SPARC are up-regulated, we hypothesized that the interaction between SPARC, IGFBP2, and MMP2 may play a pivotal role in the progression of this disease.

In conclusion, we found that stable over-expression of SATB1 in the K562 cell line affects a set of genes involved in various cellular processes, including cell differentiation, proliferation, and signal transduction. Of those aberrantly expressed genes, we concentrated on the extra-cellular matrix protein, SPARC, and discovered that SATB1 protein levels affect SPARC expression by directly binding a 17 bp sequence in the third intron. In order to further explore the interaction between SATB1 and SPARC, it will be important to identify the core region [20] within the 17 bp sequence. It is also shown that over-expression of SATB1 induces a CREB-binding protein (CBP) that binds the globin gene sequence and regulates its expression during erythroid differentiation of K562 cells [21]. Whether SATB1 regulates SPARC expression in the same mode is of great interest and awaits further study.

Acknowledgments

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