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An essential GT motif in the lamin A promoter mediates activation by CREB-binding protein ☆

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Abstract

Lamin A is an important component of nuclear architecture in mammalian cells. Mutations in the human lamin A gene lead to highly degenerative disorders that affect specific tissues. In studies directed towards understanding the mode of regulation of the lamin A promoter, we have identified an essential GT motif at −55 position by reporter gene assays and mutational analysis. Binding of this sequence to Sp transcription factors has been observed in electrophoretic mobility shift assays and by chromatin immunoprecipitation studies. Further functional analysis by co-expression of recombinant proteins and ChIP assays has shown an important regulatory role for CREB-binding protein in promoter activation, which is mediated by the GT motif.

Keywords: Nuclear lamina; Lamin A promoter; A-type lamins; CREB-binding protein

The lamin proteins are components of the nuclear lamina, a network of filaments underlying the inner nuclear membrane. The lamina is an essential structural component of the nucleus in higher eukaryotes, and is involved in the spatial organization of nuclear processes such as DNA replication and transcription [1–3]. Two major kinds of lamins are present in vertebrates. The B-type lamins (B1 and B2) are found in nearly all somatic cells, whereas the A-type lamins (A and C) are expressed primarily in differentiated cells, in a tissue- and stage-specific manner. Lamins A and C are alternatively spliced products of the lamin A (*LMNA*) gene, whereas lamins B1 and B2 are coded by separate genes. Germ cells express additional splice variants termed lamin C2 and B3. Mutations in the human *LMNA* gene have been linked to at least 10 highly degenerative disorders that mainly affect muscle, cardiac, adipose, and bone tissues, and also cause premature ageing syndromes [4,5]. Hence the regulation of lamin expression has important implications for lamin function.

The expression of the *LMNA* gene is induced upon cell differentiation and is undetectable in embryonic cells [6–8]. We have previously characterized the proximal promoter of the rat *LMNA* gene, and reported two important motifs, a GC-rich sequence at −101, which can bind to Sp1/Sp3 transcription factors, and an AP-1-binding motif at −7 that binds to c-Jun and c-Fos [9,10]. Additional motifs required for the cell-type specific transcription of A-type lamins have been identified in the first intron of the gene [11]. The 5′ flanking sequences of the mouse and human *LMNA* genes are highly homologous to the rat sequences, with total conservation of the GC motif, TATA-box, and AP-1 motif in all three species [12,13].

In this study, we have analyzed the importance of a GT motif at the −55 position of the lamin A proximal promoter (in the antisense direction) as earlier DNase I footprinting studies had revealed a footprint at this site [9]. Our functional analysis and DNA–protein-binding studies suggest that the GT motif is required for promoter activity and binds to the Sp family of transcription factors. To identify additional factors involved in lamin A promoter

☆ *Abbreviations:* CBP, CREB-binding protein; CtBP1, carboxyl-terminal-binding protein 1; EMSA, electrophoretic mobility shift assay; SL2, Schneider line 2.

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regulation, we have employed the E1A adenoviral oncogene product which has been used extensively to decipher mechanisms of gene expression. Our data suggest that E1A activates the promoter by recruitment of CREB-binding protein (CBP). Binding of CBP to the promoter resulted in acetylation of histones H3 and H4 at the promoter, as shown by chromatin immunoprecipitation analysis. Functional assays suggested that CBP upregulated promoter activity through the GT and TATTA motifs.

Materials and methods

Lamin a promoter constructs. Mutant constructs were made by PCR-based mutagenesis using the rat lamin A proximal promoter fragment spanning −114 to +15 as template. To generate the GT mutant, the mutant primer extending from −114 to −43 with the GT motif mutated from CCACCCC to CCAAAAC was used as forward primer and the segment from +15 to −19 was used as reverse primer. To generate the TATTA mutant, the −114 to −81 fragment was used as forward primer, and the +15 to −38 sequence with the TATTA motif mutated to GCTTA was used as reverse primer. The sequences of the constructs were verified by automated DNA sequencing. The amplified segments were cloned into the pGL3-Basic vector (Promega Corporation) which contains the firefly luciferase gene as a reporter but does not contain any eukaryotic promoter or enhancer elements. The construction of the wild-type promoter vector, pGL-130 (−114 to +15), and the GC and AP-1 mutants has been described earlier [9,10].

Cell culture and DNA transfections. Cell culture conditions and transient transfection assays of reporter plasmids have been described in detail earlier [9,10]. Transfections with mammalian cells were carried out using lipofectamine (Invitrogen) and 1 μg of promoter DNA (pGL-130 or mutants), 500 ng of a β-galactosidase expression vector, and 100–1000 ng of expression vectors. Transient transfections into Schneider line 2 (SL2) cells were performed using Cellfectin (Invitrogen) and 1.5 μg of promoter DNA (pGL-130 or mutants), 500 ng of a β-galactosidase expression vector, and 50 ng of *Drosophila* expression vectors (pPacSp1 or pPac Sp3, which contain full-length Sp1 or Sp3 cDNAs downstream of the actin 5C promoter; or pPac0, which lacks an insert and was added as a control). These were provided by J. Horowitz (North Carolina State University, Raleigh). Cells were lysed and aliquots were assayed for luciferase activity using a kit from Promega Corporation and for β-galactosidase activity as an internal control by a standard method. Additional expression vectors used in these studies were as follows. CBP (with an HA tag) and p300 constructs were obtained from B. Thimmapaya (Northwestern University, Chicago). E1A and its mutants were provided by J. R. Nevins (Duke University Medical Center, Durham), and M. L. Harter (Cleveland Clinic Foundation, Cleveland). Carboxyl-terminal-binding protein 1 (CtBP1) construct was obtained from G. Chinnadurai (St. Louis University, St. Louis). For treatment with roscovitine, HeLa cells were treated for 24 h with 15 μM roscovitine after 24 h of transfection with CBP and wild-type promoter. (Treatment of HeLa cells with higher concentrations of roscovitine resulted in cell death).

Electrophoretic mobility shift assays (EMSAs). EMSAs were performed with HeLa nuclear extracts and labeled double-stranded oligonucleotides (listed in Fig. 2A). A typical-binding reaction was carried out with 10,000 cpm of probe (0.01 pmol) and 5 μg of nuclear extract in 20 μl buffer containing 10 mM Tris–HCl, pH 7.5, 1 mM $MgCl_2$, 50 mM NaCl, 0.5 mM DTT, 4% glycerol, and 50 μg/ml poly (dI-dC)–poly (dI-dC) for 20 min at room temperature. In competition experiments, 100-fold molar excess of the cold competitor was preincubated with the extracts for 10 min at room temperature before the labeled fragment was added. For supershift assays, 2 μg of antibody was added to the binding reaction and incubated for 60 min at 4 °C. Antibodies to Sp1 (PEP2), Sp3 (D-20), and Sp4 (V-20) were from Santa Cruz Biotechnology. The complexes were resolved in nondenaturing 6% polyacrylamide gels in 0.5 × TBE buffer, and gels were autoradiographed overnight at −70 °C.

Chromatin immunoprecipitation (ChIP) assay. HeLa cells were fixed with 1% formaldehyde, chromatin was isolated and immunoprecipitated with antibodies to histone H3 acetylated at lys9 and lys14, or histone H4 acetylated at lys16 (Upstate Biotechnology), Sp factors, c-Jun (N) or HA tag (Y-11) (Santa Cruz Biotechnology). ChIP assays were carried out using a kit from Upstate Biotechnology as per the manufacturer's instructions. The DNA isolated from the immunoprecipitated samples was amplified by PCR using primers for the −65/+15 promoter fragment which encompasses the GT and AP-1 motifs.

Results

Requirement of the GT motif for promoter activity

In order to examine the role of the GT motif in controlling lamin A/C proximal promoter activity (promoter sequence given in Fig. 1A), this site was mutated by PCR-based mutagenesis and the mutant construct was cloned upstream of a luciferase reporter gene. Luciferase reporter assays in three differentiated mammalian cell lines indicated a loss in promoter activity of 5–7-fold compared to the wild-type construct, supporting an important role for this site in promoter regulation (Fig. 1B). As the TA TTA motif in this promoter (at −33) has a weak consensus to the canonical TATA box, the importance of this sequence was also determined by mutational analysis. The TATTA mutant displayed a substantial loss in promoter activity in various cell lines (>10-fold), consistent with its role as a bonafide TATA box.

As GT-rich sequences have been earlier shown to bind to Sp factors which are present in abundance in mammalian cells [14], we assessed the effects of exogenously expressed Sp1 and Sp3 on lamin A promoter activity in *Drosophila* SL2 cells which lack Sp factors. As observed earlier [10], the wild-type lamin A/C promoter was unable to drive reporter gene activation in the absence of Sp factors (Fig. 1C). Co-transfection with Sp1 and Sp3 expression vectors gave about 20-fold enhancement in activity. The mutated GT motif gave only 6- or 2-fold increase in activity in the presence of Sp1 or Sp3, respectively, consistent with a requirement for these factors for promoter activity. The TATTA mutant was not activated upon expression of Sp1 or Sp3.

Binding of the GT motif to Sp factors

Binding of Sp factors to the GT motif was examined by EMSAs with HeLa nuclear extracts. A strong complex 'a' was formed with the labeled GT oligonucleotide with additional minor complexes 'b' and 'c' which were competed out by 100-fold excess of unlabeled wild-type GT oligonucleotide and Sp1 consensus sequence but not by the mutated GT sequence, thus confirming the specificity of the complexes (Fig. 2). Complex 'a' was supershifted by preincubation with Sp1 antibody, whereas complexes 'b' and 'c' were depleted upon preincubation with Sp3 or Sp4 antibodies. These data confirm that the GT motif binds specifically to the Sp family of proteins. The minor complexes 'b'

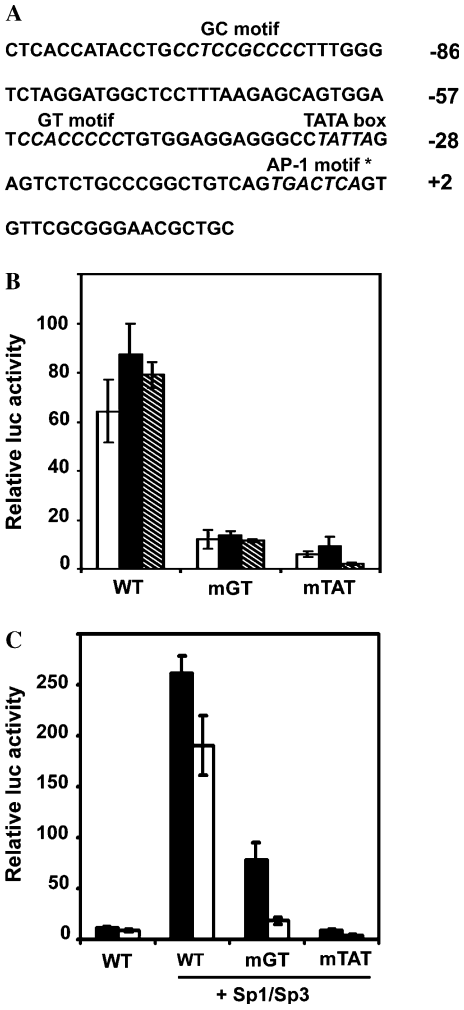

Fig. 1. Functional analysis of lamin A promoter mutants. (A) Sequence of the lamin A proximal promoter spanning −114 to +15, showing transcription factor-binding sites (in italics) and the transcription start site at +1 (asterisk). (B) Luciferase (luc) reporter gene assays of the wild-type promoter (WT), GT mutant (mGT), and TATTA mutant (mTAT), in HeLa cells (open bars), NIH 3T3 (solid bars), and COS-1 cells (hatched bars). Relative luciferase activity (mean ± SD for three experiments) was calculated as fold activation over that of pGL3-Basic vector alone after normalization for β-galactosidase activity. (C) Luciferase reporter gene assays of lamin A promoter constructs in SL2 cells, cotransfected with 50 ng of pPacSp1 (solid bars) or pPacSp3 (open bars). For the control (WT) assay, wild-type promoter was cotransfected with the empty pPac0 vector.

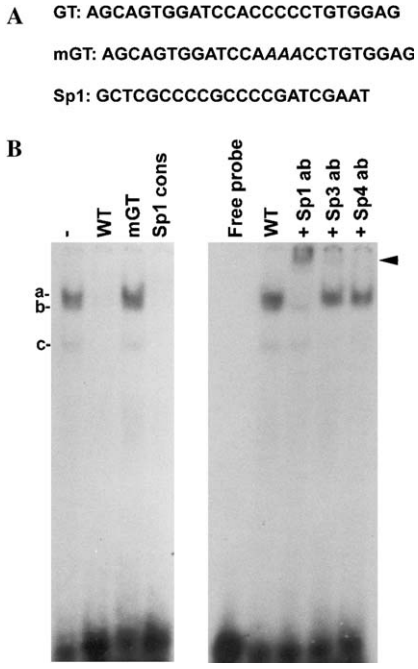

Fig. 2. EMSAs with HeLa nuclear extracts. (A) Sequences of wild-type and mutant GT oligonucleotides and Sp1 consensus. (B) Left panel, EMSAs of the labeled GT oligonucleotide in the absence (−) or presence of 100-fold molar excess of the following unlabeled competitors: wild-type GT (WT), mutant GT (mGT), or Sp1 consensus (Sp1 cons). Right panel, supershift assays with antibodies to Sp1, Sp3, or Sp4. Supershifted complex is marked by an arrow.

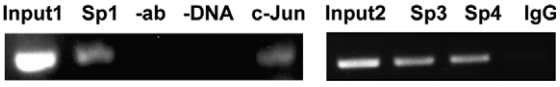

Fig. 3. ChIP assay with HeLa cell nuclei. PCR amplification of −65/+15 promoter segment with DNA isolated after ChIP assay with the indicated antibodies and controls; the DNA sample for input1 was twice the concentration of input2.

and 'c' have been earlier attributed to binding of full-length Sp3 and a shorter Sp3 fragment, respectively [15], and the GT motif might also bind to the highly homologous Sp4 factor.

Binding of Sp factors to the promoter in vivo was determined by a ChIP assay. As shown in Fig. 3, specific amplification of the −65/+15 promoter segment was obtained in the presence of antibodies to Sp1, Sp3, and Sp4 or to c-Jun as a positive control for binding to the AP-1 motif, thus confirming the binding of Sp factors to the lamin A/C promoter in HeLa cells. There was no detectable binding in a control assay with IgG alone.

Activation of promoter by CBP

The E1A adenoviral oncogene product has been used extensively to decipher mechanisms of gene expression as it has the ability to bind to important cell cycle regulators such as the retinoblastoma protein (pRb), the cyclin-dependent kinase inhibitor p21, and the coactivators CBP and p300 [reviewed in 16]. When E1A was ectopically expressed in HeLa cells along with the wild-type lamin A/C proximal promoter, there was a strong enhancement of activity by 6–8-fold (Fig. 4A). To determine the mechanism of this activation, the effects of various functional mutants of E1A on promoter activation were compared. The expression levels of the E1A mutants in Western blots and their transfection efficiencies as determined by immunofluorescence assays were observed to be approximately equivalent (data not shown). Promoter activation was least in the presence of the dl2–36 and dl38–67 amino acid deletion mutants which abrogate binding to p300, CBP, and p21. Promoter activation was also low in the presence of dl225–238 which pre-

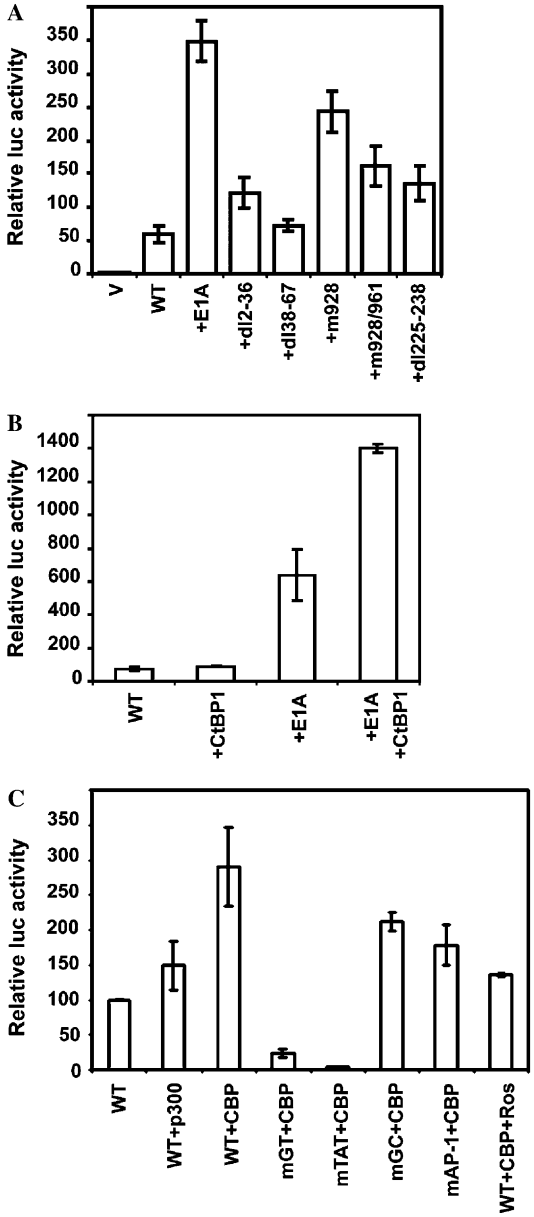

Fig. 4. Regulation of lamin A promoter activity by exogenous factors. Luciferase reporter gene assays of wild-type promoter (WT) cotransfected with (A) 100 ng E1A or mutant E1A constructs; (B) 100 ng CtBP1 and/or E1A; (C) 1 μg p300 or CBP. In (C), CBP was also cotransfected with the indicated mutant promoter constructs. Samples transfected with wild-type promoter and CBP and treated with roscovitine are indicated (WT + CBP + Ros).

vents binding of E1A to the transcriptional regulator, CtBP1 [17]. The m928 and m928/961 nucleotide point mutations, which reduce binding of E1A to pRb, also partially reduced promoter activation. However, pRb is unlikely to regulate lamin A/C promoter directly as this promoter does not have a binding site for pRb targets such as E2F. p21, not being a transcription factor, is also unlikely to directly affect the lamin A/C promoter.

The effects of some of these regulators on lamin A/C promoter activity were then determined. Ectopic expression of CtBP1 in HeLa cells did not directly alter lamin

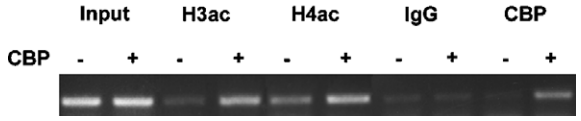

Fig. 5. ChIP analysis of lamin A promoter in CBP-transfected HeLa cells. PCR amplification of −65/+15 promoter segment with DNA isolated after ChIP assay with the indicated antibodies and controls. Samples from untransfected cells and cells transfected with CBP are indicated.

A/C promoter activity, though it enhanced E1A activation by twofold (Fig. 4B); this indirect effect may explain the lowering of activation by the dl225–238 mutant. Interestingly, ectopically expressed CBP activated the lamin A/C promoter about threefold in HeLa cells (Fig. 4C). Activation by the related coactivator, p300, was to a lesser extent (1.5-fold). As CBP/p300 are expressed abundantly in most cell types, ectopically expressed CBP/p300 generally elicit a lower response, and the specificity of the effect of CBP was initially confirmed by mutational studies. Activation by CBP was inhibited by promoter constructs bearing mutations in the GT and TATTA motifs, but was only partially affected by mutations in the GC or AP-1 sites. This suggested that the GT and TATTA motifs might mediate activation by CBP. In addition, the specificity of CBP activation was examined by using the inhibitor roscovitine which inhibits cyclin-dependent kinase activity. Roscovitine blocks cyclin E-cdk2 activity, which is necessary for the phosphorylation and subsequent activation of the histone acetyltransferase activity of CBP [18]. Treatment of cells transfected with CBP and the wild-type promoter with 15 μM roscovitine resulted in inhibition of CBP-mediated activation of the promoter (Fig. 4C).

CBP has been shown to activate promoters by acetylation of histones around the target sequence [19]. In order to determine whether CBP can acetylate histones H3 and H4 at the lamin A proximal promoter, a ChIP assay was carried out with antibodies to histone H3 acetylated at lys9, lys14 and histone H4 acetylated at lys16, which are the major species of acetylated histones involved in gene activation. As shown in Fig. 5, there was several-fold enrichment of acetylated H3 and about twofold enrichment of acetylated H4 in cells ectopically expressing CBP compared to untransfected cells, thus confirming histone acetylation by CBP at the lamin A proximal promoter. Furthermore, binding of CBP to the lamin A promoter was confirmed in a ChIP assay with antibody to ectopic CBP. A control ChIP assay with normal rabbit IgG showed only background signal, thus validating the specificity of the assay. Increase in histone acetylation was not observed in a ChIP assay with cells ectopically expressing p300 (data not shown).

Discussion

In this study, we have shown that the GT-rich motif at the −55 position of the rat lamin A proximal promoter is required for optimal promoter activity by mutational

analysis in various cell lines. EMSAs indicated that this motif binds to the Sp family of proteins, which was also confirmed by ChIP analysis with antibodies to Sp factors. Hence, the lamin promoter is comprised of two Sp-factor binding sites, the GT sequence and the earlier characterized GC motif [10]. There are a number of promoters that harbor multiple Sp-factor binding sites and do not require a TATA box for formation of the pre-initiation complex [20]. However, our mutational analysis indicates that the TATTA motif at the −33 position of the lamin A promoter functions as an authentic TATA box. In addition, primer extension assays described in earlier studies have shown that the lamin A transcript is initiated at a single start site [9,12], and multiple start sites that are characteristic of TATA-less promoters have not been observed. Our functional studies suggest that the GT and GC motifs might control the lamin promoter in distinct ways. We propose that the GT motif is essential for lamin A proximal promoter activity and functions through the coactivator CBP. On the other hand, based on our earlier mutational studies with GC/AP-1 double mutants in mammalian cells [9,10], we suggest that the GC and AP-1 motifs act together in regulating promoter activity upon availability of AP-1, which is transiently expressed in dividing cells. It may be noted that both GC and GT are required for lamin A promoter activity under limiting amounts of Sp factors in SL2 cells [10; this study]. However, in the presence of abundant Sp factors in mammalian cells, there is substantial loss in activity with the GT mutation but not with the GC mutation, suggesting differences in binding interactions at these two motifs [9; this study].

We have identified a role for CBP in lamin promoter activation by employing the E1A oncogene product in functional assays. Mutations in the GT and TATTA motifs prevented this activation, which is consistent with the 'bridging' coactivator role of CBP between a regulatory transcription factor and components of the basal transcription machinery. The specificity of CBP activation was confirmed by ChIP analysis which demonstrated an increase in acetylation of histones H3 and H4 at the lamin A promoter. The activation of the promoter by E1A may be explained by proposing that E1A recruits CBP to the promoter, as previous studies have shown that E1A can regulate gene expression through its CBP/p300 binding domain [16]. As the histone acetyltransferase domain of CBP is adjacent to the binding site for E1A, the histone acetyltransferase activity of CBP is retained when it is complexed with E1A [19]. CBP and p300 are highly homologous transcriptional coactivators containing histone acetyltransferase activity, and can cooperate with various transcription factors including Sp1 to control gene expression [21]. CBP and p300 can generally complement each other in various functions, though distinct roles have been observed under certain conditions [21,22]. The lamin A promoter might preferentially require CBP as p300 enhanced promoter activity to a lower extent. Our data also provide a possible mechanism for the observed GT-mediated retinoic acid induction of the lamin A promoter in embryonic cells [23], since CBP is known to interact with retinoic acid receptors [21].

In summary, our studies have shown that the GT motif is an important determinant of lamin A promoter activity and binds to the Sp family of transcription factors. Furthermore, the GT site mediates activation through the coactivator CBP.

Acknowledgments

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