Stra13 Homodimers Repress Transcription through Class B E-box Elements*

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A mammalian basic helix-loop-helix protein known variably as Stra13, Sharp2, and Dec1 has been implicated in cell activation, proliferation, and differentiation. Indeed, Stra13 null mice develop age-induced autoimmunity as a result of impaired T-lymphocyte activation, leading ultimately to the accumulation of autoreactive T-cells and B-cells. Stra13 is expressed in embryonic as well as adult tissues derived from neuroectoderm, mesoderm, and endoderm and has been associated with response to hypoxia, suggesting a complex role for this protein and the highly related Sharp1/Dec2 protein in homeostatic regulation. Whereas Stra13 is known to regulate many important cellular functions and is known to cross-regulate biological responses to other basic helix-loop-helix containing transcription factors, including c-Myc and USF, it is unclear if this protein binds directly to DNA. Indeed, the basic domain of Stra13 contains a proline residue at an unprecedented position. Herein, we have determined that Stra13 binds with high affinity to CACGTG class B E-box elements as a homodimer with preference for elements preceded by T and/or followed by A residues. In addition, transient transfection experiments reveal that Stra13 represses transcription when bound to these and related sites. Our data suggest that Stra13 regulates cellular functions through antagonism of E-box activator proteins and also through active repression from E-box elements.

Basic helix-loop-helix proteins represent a large and diverse class of transcription factors implicated in cell fate specification, cell proliferation, apoptosis, metabolism, and cell activation (1). The Stra13, Sharp2, Dec1 basic helix-loop-helix transcription factor has been identified in a number of biological contexts (for simplicity we will refer to this protein as Stra13).

For example, Stra13 was identified as a retinoic acid-inducible gene that promotes neuronal differentiation in P19 embryonal carcinoma cells (2). In addition, Stra13 and a related protein, Sharp1/Dec2, were identified in a degenerate PCR screen for bHLH proteins expressed in the adult rat brain (3). Interestingly, Stra13 and Sharp1/Dec2 were both induced as immediate early genes in cultured PC12 pheochromocytoma cells treated with nerve growth factor, and Stra13 was rapidly induced by glutamate stimulation throughout the rat cerebral cortex (3). This gene was also identified as a cAMP-inducible transcript in differentiating chondrocytes (4) and was later found to be cAMP-inducible in many cell types (5). More recent work has described Stra13 induction following T-cell activation (6), tyrosine kinase receptor signaling (7), hypoxia (8–10), and even serum starvation (11). Taken together, these data indicate that Stra13 expression is closely associated with activation and stress in many cell types.

Recently, Sun et al. (6) have used gene targeting to generate Stra13−/− mice. Surprisingly, homozygous Stra13 mutant mice are born and survive to adulthood. However, aging Stra13 mutant mice develop an autoimmune disorder. This effect has been traced to impaired CD4+ T-cell activation, with reduced interleukin-2 production, reduced clonal expansion, impaired T-cell differentiation, and reduced clearance of activated lymphocytes (6). Despite indications that Stra13 may regulate activation and stress in a number of cell types, Stra13-binding DNA elements have yet to be identified. Consequently, the effect of this transcription factor on its theoretical DNA target(s) is also unknown. The putative Stra13 DNA-binding/dimerization domain is somewhat related to bHLH domains of enhancer of split family (E(spl))/Hes transcriptional repressor proteins. However, Stra13 contains a proline residue in a distinct location within the basic domain. Therefore it is not clear whether Stra13 even binds directly to DNA. In addition, a fusion construct between the GAL4 DNA-binding domain and Stra13 can repress transcription from GAL upstream activator sequence sites through the recruitment of a histone deacetylase and perhaps through direct effects on the basal transcription factor TFII B (2, 11). However, it is not clear whether Stra13 functions as a DNA-binding repressor, a co-repressor, or perhaps even a transcription activating protein that is behaving inappropriately when fused to GAL4 (12). Indeed, the conformation of a GAL4-Stra13 fusion protein on DNA would be dramatically different from the conformation of Stra13 bound through its own putative DNA-

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1 The abbreviations used are: bHLH, basic helix-loop-helix; EMSA, electrophoretic mobility shift assay; BSA, bovine serum albumin; wt, wild type; PBS, phosphate-buffered saline.
binding domain. Consequently, the biochemical mechanism by which Stra13 functions remains unknown. Here we report identification of the Stra13 DNA target site, the well-described CACGTG E-box element, with preference for this site preceded by T and/or followed by an A residue. In addition we have determined that Stra13 can function as a homodimer to repress transcription from these sites. These data identify Stra13 as a transcriptional repressor protein that functions to regulate E-box elements through cross-interference with E-box-binding transcriptional activators that bind such sites and through direct transcriptional repression from the class B E-box and related sites.

EXPERIMENTAL PROCEDURES

Cell Culture— COS-7 cells were maintained in Isco’s medium supplemented with 10% fetal bovine serum, whereas HC11 cells were maintained in RPMI 1640 supplemented with epidermal growth factor (10 ng/ml), insulin (5 μg/ml), and 10% fetal bovine serum (13, 14).

Transfections—For transfections, HC11 or COS-7 cells were seeded at a dilution of 1:20 (60-mm plates) or 1:30 (6-well plates) in their respective media. Transfections were carried out using the Superfect (Qiagen) transfection reagent according to manufacturer’s specifications. Typically, for 60-mm cell cultures 4–6 and 10–12 μg of total DNA were used for COS-7 and HC11 cells, respectively. Cells were lysed 36–48 h post-transfection using ice-cold 1× Triton X-100 lysis buffer (50 mM Hepes, pH 7.4, 150 mM NaCl, 10% glycerol, 1% Triton X-100, 1 mM EGTA, 1 mM phenethylmethylsulfonyl fluoride, 10 μM aprotinin, and 10 mM NaF). Soluble and insoluble fractions were separated by centrifugation at 13,200 rpm for 15 min at 4°C.

Plasmid Vectors— Murine Stra13 was cloned from mammary gland cDNA through a combination of reverse transcriptase PCR and high stringency hybridization based on the identification of an expressed sequence tag sequence, which at the time represented a fragment from a novel bHLH domain containing cDNA.2 The Stra13 constructs described in the following section were subcloned into pcDNA3 for expression in transfected COS-7 and HC11 cells (Invitrogen). FLAG-StrA13 and Stra13-Myc were created using PCR to add an in-frame epitope tag at the N- and C-terminal ends, respectively, of the Stra13 open reading frame. The resulting linked mutant cDNA fragment in pcDNA3 was used to replace the corresponding wt N-terminal Stra13 sequence with the FLAG epitope-tagged amino acids 1–49 and amino acids 67–136 of the Stra13 basic domain with the Stra13 C-terminal basic N-terminal fragment with the Stra13 C-terminal basic domain.

Luciferase Assays— For transfections, HC11 or COS-7 cells were seeded in 60-mm plates and transfected with 500 ng of test luciferase reporter vector along with increasing amounts of pcDNA3 vector expressing either wt or mutant Stra13. In each case the observed luciferase activity for each transfected sample was corrected according to the β-galactosidase activity generated from a co-transfected Rous sarcoma virus- or cytomegalovirus-lacZ vector. The average luciferase activity and the deviation of the duplicate samples for each condition were plotted. The average activity observed in the absence of co-transfected Stra13-expressing construct was given a relative value of 100%. For each experiment, levels of ectopic Stra13 protein were determined through immunoprecipitation/Western blot analysis on duplicate samples.

β-Galactosidase Assays— For experiments shown in Figs. 3 and 4, COS-7 cells or HC11 cells were transfected with 100 ng (Fig. 3, A–D), 1 μg (Fig. 3, E and F), or 5 μg (Fig. 4) of luciferase reporter vectors and pcGL3-(tCACGTGa)-SV40, or pcGL3-(tCACGTGa)-SV40, or pcGL3-(tCACGTGa)-SV40 were co-transfected (15) in the absence or presence of increasing amounts of pcDNA3 vector expressing either wt or mutant Stra13. Each experiment was performed in triplicate.
translated Stra13 could bind to N-box elements (specifically CACGAG). This occurred in the absence of BSA and poly(dI/dC) nonspecific competitors. This low affinity Stra13 N-box complex was used as a molecular weight marker to purify specific Stra13 complexes from EMSA gels in the early rounds of our site selection protocol. After three rounds of Stra13 binding, EMSA gel purification of bound oligonucleotides, and PCR amplification we had enriched high affinity Stra13-binding sites to a level where we would detect radiolabeled Stra13-DNA complexes on the EMSA gel. The Stra13-bound DNA pool was amplified by PCR, cloned, and sequenced (16). This revealed enrichment for one type of 6-nucleotide site in 23 of 26 clones that contained the predicted 70-nt insert (Table I). Interestingly, the Stra13 binding site identified in our screen was CACGAG, which is a class B E-box element (20). In addition, the CACGAG sequence was frequently preceded by a T residue and followed by an A residue, although these are not absolutely required for high affinity binding (see below).

To test for the importance of individual bases on Stra13 binding to the E-box identified in our screen, we performed EMSA assays to test for binding to tCACGAGC sites (probe 2) under high stringency conditions in the presence of BSA and poly(dI/dC) (Fig. 2A) (21). This element bound a protein or proteins present in the control in vitro transcription/translation reaction. However, when the in vitro transcription/translation reaction was programmed with a Stra13-FLAG epitope-tagged cDNA and this was incubated with probe 2, a novel Stra13-containing complex was formed that could be super-
Shifted through inclusion of anti-FLAG monomeric antibody. The anti-FLAG antibody did not supershift control complexes. We next tested for formation of Stra13 complexes on related sites. For example, we determined whether Stra13 bound to tCACGTGc and gCACGTGc to test for the importance of residues within the selected E-box consensus and for the importance of flanking T and A residues that were selected in our screen. Interestingly, Stra13 formed a specific complex with tCACGTGc as determined by the supershift of this complex in the presence of anti-FLAG antibody in the binding reaction. This site has a single mutation in the core E-box but with optimal flanking residues. In contrast, Stra13 did not form complexes with gCACGTGc, which has the same E-box core mutation but without flanking T and A nucleotides. Next, we studied Stra13-DNA interactions by testing whether various E-box elements could compete Stra13 off of probe 2, tCACGTGc. Unlabeled excess tCACGTGc (probe 2), tCACGTGc (probe 1, not shown), gCACGTGc (probe B1, not shown), and gCACGTGc (probe B2, not shown) diminished radioactive Stra13-probe 2 complex formation (Fig. 2B and data not shown). Interestingly, excess unlabeled CAGGTG elements including tCACGTGc (mutant probe M1), gCACGTGc (probe A1), and gCACGTGc (probe A2) did not compete for Stra13 from labeled probe 2 (Fig. 2B and data not shown). In addition, the single mutant gCACGTGc element (hairpin probe) (data not shown) and mutant E-box elements that differ from the CACGTG consensus by 2 nucleotides could not compete with probe 2 for binding to Stra13 (Fig. 2B and data not shown). Thus, Stra13 binds with high affinity to CACGTG elements. It can also bind to single mutant CAGGTG elements, although only when these elements are surrounded by optimal flanking residues (Fig. 2A) and only with significantly lower affinity than CACGTG elements (this element did not compete for Stra13 binding in Fig. 2B).

### Stra13 activates or represses transcription from its cognate DNA target site

#### TABLE I

*Consensus sequences binding to Stra13 homodimers*

| Consensus | -7 -6 -5 -4 -3 -2 -2 2 3 4 5 6 7 |
|-----------|---------------------------------|
| G         | T 3 10 5 - - - - - - 0 8 5 6 4 |
| A         | T 4 9 2 17 - - - - - - - 1 6 5 6 |
| C         | 9 9 8 1 - - - - - - 3 9 9 4 |

#### FIG. 2

*Sta13 binds to CACGTG E-box elements.* A. Electrophoretic mobility shift assay using radiolabeled tCACGTGc, tCAGGTGc, or gCACGTGc-containing probes in the presence or absence of FLAG-Sta13 protein. The formation of specific FLAG-Sta13-DNA complexes was confirmed by supershifting of complexes in the presence of anti-FLAG antibody (indicated with an *). B, the affinity of FLAG-Sta13 for tCACGTGc elements was tested by competition using excess non-radiolabeled tCACGTGc, tCAGGTGc, or gCACGTGc sequences as indicated.

#### Stra13 activates or represses transcription from its cognate DNA target site, three copies of the tCACGTGc element were inserted upstream of the minimal and thymidine kinase promoters in the luciferase vectors pGL3 and pGL3-TK, respectively. These constructs were transfected into COS-7 cells that do not express detectable Stra13 protein and also into HC11, a mouse mammary epithelial line that expresses endogenous Stra13. The addition of E-box elements dramatically increased the luciferase activity generated by these vectors in both lines (Fig. 3, A and C), presumably because of the expression and effect of endogenous E-box-binding transcription-activating proteins. Cotransfection of FLAG-Sta13 repressed expression of either promoter in a dose-dependent fashion (Fig. 3, A and C). Interestingly, the N-terminal FlaG-Sta13-(1-143) bHLH domain construct was as active as full-length Sta13 in repressing transcription in these assays, suggesting that repression was occurring as a result of Stra13 proteins competing with endogenous E-box-activating proteins for access to CACGTG elements. This indicates that repression by Stra13 involved competition with endogenous E-box binding transcription factors for target CACGTG elements. We determined whether FLAG-Sta13 (Δbasic) and FLAG-Sta13 (acridine) mutants could function as repressors in this system. Basic domain mutants were totally unable to repress transcription from the CACGTG elements at concentrations where wild type Stra13 inhibited transcription by ~90% (2 µg) (Fig. 3, B and D). This
Fig. 3. Competitive repression by Stra13 through class B (CACGTG) E-box elements. COS-7 cells (A, B, and E) or HC11 cells (C and D) were transfected with luciferase reporter vector along with increasing amounts of a pcDNA3 vector expressing either wild-type Stra13 or mutant Stra13, or both, as indicated. The observed luciferase activity for each transfected sample was corrected according to the β-galactosidase activity generated from a co-transfected lacZ vector (see “Experimental Procedures”). E, COS-7 cells were transfected with pG3-(tCACGTGa)₃ luciferase reporter vector in the presence or absence of 0.1 µg of pcDNA3-FLAG-Stra13 vector. To test the ability of the Stra13 basic domain mutants to act as
effect was associated with disruption of DNA binding as both proteins were stable (Fig. 1C) and found in the nucleus (Fig. 1D). To test whether the basic domain mutant proteins could function to sequester wild type Stra13 away from E-box elements, we cotransfected Stra13 together with FLAG-Stra13(acidic). The repressor function of wild type

dominant negative alleles by relieving the repression induced by ectopic expression of wt Stra13, increasing amounts of pcDNA3-FLAG-Stra13(Δbasic) or pcDNA3-FLAG-Stra13(Δacidic) were also cotransfected. For all panels the levels of ectopic Stra13 protein are shown by immunoprecipitation/Western blot analysis for duplicate samples transfected with 4 μg of pcDNA-Stra13 expression constructs.
StrA13 was blocked by coexpression of either of these dimerization-competent mutant proteins (Fig. 3E).

We next tested whether StrA13 could actively repress transcription in the context of a complex promoter. Insertion of two copies of the tCACGTGa element upstream of the SV40 promoter in the pGL3-SV40 luciferase vector did not affect gene expression in COS cells (Fig. 4A). Co-transfected StrA13 inhibited transcription of this CACGTG-containing promoter in a dose-dependent manner but did not repress the parental pGL3-SV40 reporter (Fig. 4A). To test whether specific E-box elements were required for StrA13-mediated transcriptional repression we inserted three StrA13 mutant binding sites, tCATATGa, tCACGGAa, and tCACGTGa, into the pGL3-SV40 reporter. Interestingly, the single nucleotide mutant site tCACGTGa was still StrA13-responsive (Fig. 4B), consistent with the fact that tCACGTGa elements bound StrA13 in vitro (Fig. 2A). In contrast, the double nucleotide mutant elements tCATATGa and tCACGGAa that did not bind StrA13 in vitro were not responsive to StrA13 in vivo. Repression from E-box elements required an intact basic domain in StrA13, because it was not observed when FLAG-StrA13(Δbasic) or FLAG-StrA13(acidic) mutants were co-transfected with pGL3-(tCACGTGa)2-SV40-Luc (Fig. 4C). In addition, this effect represented active repression because in contrast to the competitive repression observed on minimal promoters (Fig. 3) repression of the SV40 promoter required sequences in the C-terminal 268 residues of StrA13 (data not shown). To define sequences in StrA13 responsible for active repression of the SV40 promoter in this context, we generated and cotransfected a series of C-terminal truncation mutants (Fig. 4, D and E). The C-terminal boundary of the transcriptional repression domain was mapped to lie between residues 322 and 333, because C-terminal truncation mutants including FLAG-StrA13(1–333) were potent repressors, whereas FLAG-StrA13(1–322) and smaller C-terminal truncation mutants had lost this activity (Fig. 4D). The inability of FLAG-StrA13(1–322) to repress transcription was not caused by a lack of expression of this mutant protein (Fig. 4D).

StrA13 is a bHLH protein associated with cell activation and stress in many tissues. Indeed, this protein is induced in activated neuronal cells, chondrocytes, T-cells, fibroblasts, and a number of cancer cell lines. Recent genetic analysis has revealed that StrA13 is required for T-cell activation and regulation of lymphocyte clearance (6). In addition, StrA13 has recently been implicated in hypoxia-induced repression of adipogenesis (22). Despite the importance of StrA13 in these biological processes, the biochemical mechanism by which it functions remains unknown. For example, it had yet to be determined whether StrA13, which includes a conserved proline residue at an unprecedented site within its basic domain, binds directly to DNA. We have used a non-biased screen to determine that StrA13 binds to a specific DNA element, the CACGTG class B E-box element, with preference for sites preceded by T and followed by A. Following submission of this work, Zawel et al. (23) have recently reported that human StrA13 binds CACGTG elements in vitro and can repress transcription from reporter containing these sites. Such sites regulate expression of many genes associated with proliferation, differentiation, and cell activation. We have also determined that StrA13 can actively repress transcription of promoters that contain class B E-box elements. The domain of StrA13 responsible for transcriptional repression from CACGTG elements maps to sequences in the N-terminal 333 amino acids of StrA13. This result is consistent with data from Boudjelal et al. (2) who used GAL4-StrA13 chimeras to repress transcription from upstream activator sequence sites and to map a repression domain between amino acids 147 and 354. In addition, Sun and Taneja (11) have determined that HDAC1 and NcoR bind to StrA13 sequences between amino acids 111 and 343. Interestingly, the StrA13 deletion mutant StrA13(1–322) that failed to repress transcription (Fig. 4) still bound HDAC1, suggesting that StrA13 may mediate transcriptional repression via multiple mechanisms (data not shown).

These results are important given that StrA13 binds to and antagonizes USF proteins (24) and represses expression of c-Myc (11), two classes of bHLH-ZIP transcription activating proteins that bind to CACGTG E-box elements. StrA13 also represses expression of its own promoter through a mechanism requiring histone deacetylase activity (11). Interestingly, the StrA13 promoter contains three CACGTG elements located 261, 1125, and 2901 bases upstream of the first transcribed nucleotide (25). Recent work has identified the PPARγ2 gene as a target of StrA13-mediated transcriptional repression during hypoxia-induced suppression of adipogenesis (22). Interestingly, the promoter element that responds to StrA13-mediated repression contains binding sites for C/EBP bZIP proteins but no obvious E-box elements like those identified in our study. In addition, the bHLH domain of StrA13 was sufficient to repress expression of PPARγ2. Perhaps StrA13 represses PPARγ2 expression and adipogenesis through direct inhibition of C/EBP function. Future studies will be necessary to resolve the mechanism by which StrA13 represses expression of StrA13 and PPARγ2 promoters and to identify E-box elements in the genome that are subject to regulation by StrA13 and the StrA13-related protein, Sharp1/Dec2. Indeed, the StrA13-binding-responsive E-box elements identified in this study are likely to represent critical nodes in a competitive network of activator and repressor proteins controlling cell activation, proliferation, and stress.

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REFERENCES
1. Massari, M. E., and Murre, C. (2000) Mol. Cell. Biol. 20, 429–440
2. Boudjelal, M., Taneja, R., Matsubara, S., Bouillet, P., Dolle, P., and Chambon, P. (1997) Genes Dev. 11, 2052–2065
3. Rossner, M. J., Derr, J., Goss, P., Schwab, M. H., and Nave, K. A. (1997) Mol. Cell Neurosci. 9, 460–475
4. Shen, M., Kawamoto, T., Yan, W., Nakamasu, K., Tamagami, M., Koyano, Y., Noshir, M., and Kato, Y. (1997) Biochem. Biophys. Res. Commun. 236, 294–298
5. Shen, M., Kawamoto, T., Teramoto, M., Makihira, S., Fujimoto, K., Yan, W., Noshir, M., and Kato, Y. (2001) Eur. J. Cell Biol. 80, 329–334
6. Sun, H., Lu, B., Li, R. Q., Flavell, R. A., and Taneja, R. (2001) Nat. Immunol. 2, 1040–1047
7. Fambrough, D., McClure, K., Kuzlauskas, A., and Lander, E. S. (1999) Cell 97, 727–741
8. Wyckoff, C. C., Pugh, C. W., Maxwell, P. H., Harris, A. L., and Ratcliffe, P. J. (2000) Oncogene 19, 6297–6305
9. Ivanova, A. V., Ivanov, S. V., Danilkovich-Miagkova, A., and Lerman, M. I. (2001) J. Biol. Chem. 276, 15306–15315
10. Yoon, D. Y., Buchler, P., Saarikoski, S. T., Hines, O. J., Reber, H. A., and Hankinson, O. (2001) Biochem. Biophys. Res. Commun. 288, 882–886
11. Sun, H., and Taneja, R. (2000) Proc. Natl. Acad. Sci. U. S. A. 97, 4658–4663
12. Ruden, D. M., Ma, J., Li, Y., Wood, K., and Ptashne, M. (1991) Nature 350, 250–252
13. Warthmann, M., Celia, N., Hofer, P., Groner, B., Xu, K., Hennighausen, L., and Hynes, N. E. (1996) J. Biol. Chem. 271, 31863–31868
14. Ball, R. K., Friis, R. R., Schonenberger, C. A., Doppler, W., and Groner, B. (1988) EMBO J. 7, 2085–2095
15. Krylov, D., Kasai, K., Echlin, D. R., Taparowsky, E. J., Arnheiter, H., and Vinson, C. (1997) Proc. Natl. Acad. Sci. U. S. A. 94, 12274–12279
16. DeCicco, V., Tini, M., Fleck, G., Oug, E., Evans, R. M., and Oubalakowski, G. (1994) Genes Dev. 8, 538–553
17. Dear, T. N., Hainsl, T., Follio, M., Nehls, M., Wilmore, H., Matena, K., and Buchan, T. (1997) Oncogene 14, 891–898
18. Tietze, K., Oellers, N., and Kruitt, E. (1992) Proc. Natl. Acad. Sci. U. S. A. 89, 6152–6156
19. Oellers, N., Dehio, M., and Kruitt, E. (1994) Mol. Gen. Genet. 244, 465–473
20. Dang, C. V., Dolde, C., Gillison, M. L., and Kato, G. J. (1992) Proc. Natl. Acad. Sci. U. S. A. 89, 599–602
21. Jennings, B. H., Tyler, D. M., and Bray, S. J. (1999) Mol. Cell. Biol. 19, 4600–4610
22. Yun, Z., Maecker, H. L., Johnson, R. S., and Giaccia, A. J. (2002) Dev. Cell 2, 331–341
23. Zawel, L., Yu, J., Torrance, C. J., Markowitz, S., Kinzler, K. W., Vogelstein, B., and Zhou, S. (2002) Proc. Natl. Acad. Sci. U. S. A. 99, 2848–2853
24. Dhar, M., and Taneja, R. (2001) Oncogene 20, 4750–4756
25. Teramoto, M., Nakamasu, K., Noshiro, M., Matsuda, Y., Gotob, O., Shen, M., Tsutsui, S., Kawamoto, T., Iwamoto, Y., and Kato, Y. (2001) J. Biochem. (Tokyo) 129, 391–396
