Role of Zinc Finger Domains of the Transcription Factor Neuroni
restrictive Silencer Factor/Repressor Element-1 Silencing Transcription Factor in DNA Binding and Nuclear Localization*

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The transcription factor neuron-restrictive silencer factor/repressor element-1 (RE-1) silencing transcription factor (NRSF/REST) contains nine zinc finger domains and binds to the DNA element, neuron-restrictive silencer element/repressor element-1. REST4, a C-terminally truncated form of NRSF/REST, contains the five N-terminal zinc fingers and binds weakly to DNA yet is transported into the nucleus. To study the contribution of zinc fingers 6–8 to DNA binding, each was mutated. A mutation in zinc finger 6 or 8 had little effect; however, mutation of zinc finger 7 diminished DNA binding. Mutations in any two of these zinc fingers eliminated DNA binding. The contribution of zinc fingers 2–5 to nuclear targeting was studied. Deletion of zinc finger 5 prevented nuclear targeting. Mutations in zinc finger 2, 4, or 5 did not abolish nuclear targeting. However, a zinc finger 3 mutation together with a zinc finger 2 mutation localized to the nuclear envelope. A zinc finger 3 mutation alone or in combination with a zinc finger 4 or 5 mutation produced a punctate nuclear distribution. These results suggest the presence of signals for nuclear targeting, for nuclear entry, and for release from the translocation machinery within zinc fingers 2–5 of REST4.

Recent studies have established that one mechanism for the maintenance of the neuronal phenotype is through repression of neuronal gene expression in nonneuronal tissues (1, 2). Thus, a number of neuron-specific proteins including choline acetyltransferase (3), synapsin I (4), SCG10 (5), the type II sodium channel (6), the N-methyl-D-aspartate receptor (7) and NMDA receptor (8), the sodium channel (6), and the choline N-acetyltransferase (9), are expressed at low levels in mature neurons of adult brain (11). These splice variants contain an insertion between zinc finger domains 5 and 6 that leads to truncated proteins containing only five of the nine zinc finger domains found in NRSF/REST. We previously suggested that, at least in PC12 cells, one of these isoforms, REST4, regulates cholinergic gene expression. The mechanism appears to involve formation of hetero-oligomers between REST4 and NRSF/REST, which prevents binding of NRSF/REST to the NRSE/RE-1 sequence (12). To further study the function of NRSF/REST and REST4, we have prepared and studied deletion constructs as well as constructs containing point mutations that cause disruption of the structure of individual Cys2-His2 type zinc finger domains. The results of these studies suggest that proper zinc finger structure is important for DNA binding as well as for nuclear localization.

EXPERIMENTAL PROCEDURES

Materials—Deoxyribonucleotides, Dulbecco’s modified Eagle’s medium, and fetal bovine serum were obtained from Life Technologies, Inc. Oligonucleotide primers were synthesized with a Beckman Oligo1000 DNA synthesizer or purchased from commercial sources. [γ-32P]ATP was from ICN (Irvine, CA). The BCA protein assay kit was obtained from Pierce. Poly(dI-dC)·poly(dI-dC) was obtained from Amersham Pharmacia Biotech. The ECL Western blotting detection system and Hybond membranes were purchased from Amersham Pharmacia Biotech. Effectene transfection reagent and Qiagen plasmid kit were obtained from Qiagen Inc. (Valencia, CA). The pCDNA3 expression vector was obtained from Invitrogen (Carlsbad, CA), while pEGFP and pCMVβ were obtained from CLONTECH (Palo Alto, CA). All other reagents were from Sigma and were of the highest quality available.

Construction of Plasmids—Constructs containing green fluorescent protein (GFP) fused to REST4 were generated by subcloning the HindIII-BamHI fragment of corresponding full-length FLAG-REST4 constructs into pEGFP. Mutations were generated by the QuickChange site-directed mutagenesis kit (Stratagene, La Jolla, CA) using NRSF/REST or GFP-REST4 as the DNA template and the following oligonucleotide primers: 5′-C AAA GCC CCC ATC GCC CCT GCC CTC TGT GGC TAC-3′ and 5′-GTA GCC ACA GGC GTC AGC GGC GAT GGC GCC TTT G-3′ (for Z2mut), 5′-GAG CCC ATC TAC AAG CGT ATC ATC and 5′-GG AAA GTG TAC ACC CGT AGC AGC-3′ (for Z5mut). The abbreviations used are: NRSF, neuron-restrictive silencer element; RE-1, repressor element-1; NRSF, neuron-restrictive silencer factor; REST, RE-1 silencing transcription factor; X-gal, 5-bromo-4-chloro-3-indolyl β-D-galactopyranoside; GFP, green fluorescent protein; PBS, phosphate-buffered saline; EMSA, electrophoretic mobility shift assay(s).

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density of 10^5 cells/coverglass on the day before transfection. The cells
were plated on 100-mm^2 glass cover slips at a ratio of 1:100 (Z2S, 5'-GAT GGA CTA CAA GGA CCG CAA GGC CAC CAT CGG TCA CGC TTG 3'; Z5AS, 5'-GCG CCG TCT CGT TGA GTG TGG GT-3'; Z7mut, 5'-CTT AAA TGG CTC CTC-3' for Z6mut, 5'-CCT AAA CCT TAT AAT CTT AGT CGT CAC GGC AGG TGT GAA TTG-3' for Z7mut). Underlined nucleo-
tides denote changes introduced (Cys to Arg). The identities of the plasmid constructs were verified by the sequencing method using Sequenase (U.S. Biochemical Corp.). For the preparation of β-galacto-
sidase fused to zinc finger domains 2–5 (Z2,5mut) and to zinc finger domains 2–4 (Z2,4,5), appropriate fragments were amplified by the polymerase chain reaction from an NRSF/REST template. Primers used were as follows: Z2S, 5'-GAT GGA CTA CAA GGA CCG CAA GGC CAC CAT CGG TCA CGC TTG-3'; Z2AS, 5'-GCG CCG TCT CGT TGA GTG TGG GT-3'; Z5AS, 5'-GGG ACG GTT GAA CTG CCG TGG-3'; Z6mut, 5'-GAT GAG TGC AAT TAT G-3'; Z7mut, 5'-ATA CGG GCG TTC-3'; and 5'-GTA GTC AAT TAT G-3'; and 5'-GTA GTC ACA GTG CGG AGC ATT AAG AGG TTT AGG-3' (for Z7mut), 5'-CCA CCG CAG TTC AAC CCG CCC GTG TGT GAC TAC-3'. The amplified products were cloned into the Smal site of pBSKK. A HindIII/BamHI fragment was cloned into β-galactosidase-pcDNA3. The latter was created by inserting the β-galactosidase gene from pCMV (CLON-TECH) into the NotI site of pcDNA3. The preparation of deletion mut-
ients was as described in Lee et al. (13).

**Cell Culture and Transfection—** HEK293 cells were maintained in Dulbecco's modified Eagle's medium supplemented with 2 mM glutamine, 1 mM sodium pyruvate, 100 units/ml penicillin, 100 μg/ml streptomycin, and 10% fetal bovine serum (Life Technologies, Inc.). These cells were maintained at 37 °C in a humidified atmosphere of 10% CO_2_.

**Transfections** were performed with the use of the Effectene Transfection Reagent (Qiagen) according to the manufacturer's instructions.

**Detection of GFP and β-Galactosidase—** NIH3T3 cells were cultured in Dulbecco's modified Eagle's medium supplemented with 2 mM glutamine, 1 mM sodium pyruvate, 100 units/ml penicillin, 100 μg/ml streptomycin, and 10% fetal bovine serum (Life Technologies, Inc.). GFP was observed using a Nikon E600 epifluorescence microscope (Melville, NY). For β-galactosidase staining, cells were fixed in 1% glutaraldehyde for 5 min; washed three times in PBS; soaked in 100 mM sodium phosphate, pH 7.5, 10 mM KCl, 1 mM MgCl_2, 3 mM K_2(Fe(CN))_6, 3 mM K_3(Fe(CN))_6, 0.1% Triton X-100, and 1 mM X-gal at 37 °C for 30 min; and then washed with PBS.

**Electrophoretic Mobility Shift Assays (EMSA)—** Nuclear extracts were prepared from cells as described previously (12). The probe for EMSA was made by polymerase chain reaction using the human vesicular acetylcholine transporter/choline acetyltransferase NRSE/RE-1 as a template (see Fig. 2A). DNA fragments were end-labeled with [γ-^32P]ATP using T4 polynucleotide kinase. For binding, 10 μg of nuclear protein was preincubated on ice, with or without a 100-fold excess of unlabeled competitor DNA, for 10 min in 20 μl of 20 mM HEPES (pH 7.6), 0.1% Nonidet P-40, 10% glycerol, 1 mM dithiothreitol, 2.5 mM MgCl_2, 250 mM KCl, and 2 μg of poly(dI-dC)/poly(dI-dC). Labeled oligonucleotide (100 fmol) was mixed with nuclear protein, and the mixture was incubated for 10 min at 25 °C. For supershift assays, 10 μg of nuclear protein was preincubated on ice with or without a monoclonal antibody to NRSE/REST (12C11-1) for 30 min before adding the labeled probe. The reaction mixture was loaded onto a 4% nondenaturing polyacrylamide gel with 0.25× TBE buffer and electrophoresed for 60 min at 120 V.

**Western Blot Analysis—** Nuclear extracts (10 μg) were solubilized in Laemmli sample buffer. After separation on a reducing SDS-polyacrylamide gel, proteins were transferred onto Hybond™-P membrane as described previously (12). The membrane was then incubated with anti-NRSF/REST (12C11-1), anti-FLAG, or anti-Myc monoclonal antibody followed by horseradish peroxidase-labeled goat anti-mouse antibody, and visualized using the ECL detection kit per the manufacturer's instructions.

**RESULTS**

As illustrated in Fig. 1, NRSF/REST is a transcription factor containing nine zinc finger domains; the first of these is near the N terminus and is followed by a cluster of seven zinc finger domains, with the last zinc finger domain being near the C terminus of the molecule. REST4, which is a truncated version of NRSF/REST containing only zinc finger domains 1–5, binds weakly to the NRSF/REST target sequence NRSE/RE-1 (13). This finding as well as other studies (1) suggests that zinc finger domains 2–5 are required for DNA binding, while zinc finger domains 6–8 appear to contribute significantly to the strength of the binding interaction (13). To study further the contributions of zinc finger domains 6–8, NRSF/REST constructs with combinations of point mutations in these zinc finger domains were constructed, Fig. 1. Each zinc finger structure was disrupted by introducing a point mutation where the amino acid Cys was converted to Arg in the zinc finger domain. This mutation has been shown to disrupt the structure of Cys^2-His^2 type zinc finger domains (14). Each construct was transfected into HEK293 cells, and nuclear extracts were prepared and used for EMSA with a probe containing the human vesicular acetylcholine transporter/choline acetyltransferase NRSE/RE-1 sequence (Fig. 2A). As can be seen in Fig. 2B, the EMSA shows that the binding of NRSF/REST with mutations in zinc finger domains 6, 7, and 8 (Z6,7,8mut) diminished the gel mobility shift to levels undetectable at the sensitivity of these assays. Diminished binding was also seen in double mu-
tants containing point mutations in zinc finger domains 6 plus 7 (Z6,7mut), 7 plus 8 (Z7,8mut), and 6 plus 8 (Z6,8mut). The presence of a point mutation in zinc finger domain 6 alone (Z6mut) or zinc finger domain 8 alone (Z8mut) had little or no effect on DNA binding; however, a point mutation in zinc finger domain 7 alone (Z7mut) greatly diminished DNA binding. As shown in Fig. 2C, the expression level of each construct was nearly the same as confirmed by Western blot analysis, and if anything the construct with the point mutation in zinc finger domain 7 was expressed at the highest levels. As shown in Fig. 2D, the electrophoretic mobility band was supershifted with an anti-NRSF monoclonal antibody but not by an irrelevant mon-
oclonal antibody, confirming that the electrophoretic mobility band contained NRSF/REST. Taken together, these results suggest that in addition to zinc fingers 2–5, two adjacent zinc fingers (zinc fingers 6 plus 7 or 7 plus 8) are required for maximal DNA binding.

Although the above studies demonstrate the importance of zinc finger domains 6–8 in NRSF/REST binding to DNA, previous studies have shown that the neuron-specific isoform REST4, which contains only zinc finger domains 1–5, is tar-
ged to the nucleus (15). This was a bit surprising, since it had previously been proposed that a nuclear localization domain of NRSF/REST resides in the C-terminal part of the molecule (1, 16), and this signal is clearly absent from REST4. We first tested the effect of deleting the N-terminal region of REST4, which is known to bind the transcriptional repressor mSin3 (16–18), and then a larger fragment of the N-terminal region, which contains the first zinc finger domain. Fig. 3A shows a
schematic representation of these and other truncated forms of REST4 that were studied, each containing an N-terminal FLAG epitope for ease of identification. These constructs were transiently expressed in HEK293 cells followed by fractionation of the cells into nuclear and cytosolic extracts and locating the REST4 mutant by Western blot analysis with an anti-FLAG antibody. Western blots employing an anti-Myc antibody were used as positive controls to detect endogenous Myc protein in the nucleus. As shown in Fig. 3B, cell fractionation analysis showed that deletion of the mSin3 binding region (ΔN152) or this region plus the first zinc finger domain (ΔN209) did not affect nuclear targeting. On the other hand, constructs containing deletions of zinc finger domains 3–5 (ΔC89), zinc finger domains 2–5 (ΔC151), or zinc finger domains 1–5 (ΔC173) were detected in the cytosol but not in the nucleus. These results suggest that zinc finger domains 2–5 are required for nuclear targeting of REST4 and presumably NRSF/REST.

To demonstrate the importance of zinc finger domains 2–5 in nuclear targeting in vivo, GFP was fused to REST4; to REST1 (11), which is a natural isoform lacking zinc finger domain 5; and to a C-terminally truncated mutant lacking zinc finger domains 3–5 (ΔC89). These constructs were transiently expressed in NIH3T3 cells, and their localization was determined by GFP fluorescence microscopy. As shown in Fig. 4, although REST4 was localized in the nucleus, the deletion of zinc finger domain 5 was sufficient to prevent nuclear localization. We next confirmed whether zinc finger domains 2–5 would localize a larger protein to the nucleus by fusing this region to β-galactosidase. As shown in Fig. 5, the attachment of zinc finger domains 2–5 to the N terminus of β-galactosidase (Z2,3,4,5) conferred nuclear localization in NIH3T3 cells as judged by histochemical staining of the cells with X-gal. Neither β-galactosidase alone nor a construct containing zinc finger domains...
2–4 (Z2,3,4) fused to β-galactosidase was localized to the nucleus.

To further dissect the importance of zinc finger domains 2–5 for nuclear localization of REST4, a series of constructs were generated that contained a point mutation that disrupted the conformation of the zinc finger domain. Constructs containing one, two, three, or four of these point mutations fused to GFP were prepared and are schematically represented in Fig. 6A. As shown in Fig. 6B, a single point mutation in any one zinc finger domain permitted nuclear targeting. However, as noted below, the zinc finger domain 3 mutant, although localized to the nucleus, showed an abnormal staining pattern. Similarly, combinations of double mutants involving zinc finger domains 2 and 4 (Z2,4mut), zinc finger domains 2 and 5 (Z2,5mut), and zinc finger domains 4 and 5 (Z4,5mut) all showed normal nuclear localization, as did the triple mutant involving zinc finger domains 2, 4, and 5 (Z2,4,5mut). However, all constructs containing a mutation in zinc finger domain 3 (Z3mut, Z3,4mut, Z3,5mut, Z2,3,5mut, and Z3,4,5mut), although associated with the nucleus, appeared abnormal. The zinc finger domain 3 single mutant as well as the zinc finger domain 3 plus 4 double mutant and the zinc finger domain 3 plus 5 double mutant showed nuclear staining that was punctate rather than uniform across the nucleus. A more dramatic pattern was seen with a zinc finger domain 3 mutant in combination with a zinc finger domain 2 mutation. Mutant Z2,3mut, Z2,3,4mut, or Z2,3,5mut or the construct containing mutations in all four zinc finger domains (Z2,3,4,5mut) exhibited GFP fluorescence that appeared on the surface of the nucleus rather than inside the nucleus.

DISCUSSION

NRSF/REST is a transcription factor that contains nine Cys2-His2 type zinc finger domains. It has previously been suggested that the zinc finger domains of NRSF/REST contribute to its binding to the DNA sequence known as NRSE/RE-1. REST4, which is a C-terminally truncated neuron-specific isoform of NRSF/REST, contains only the first five of the nine Cys2-His2 type zinc finger domains. Although the physiological function of REST4 remains unclear, the binding affinity of REST4 to NRSE/RE-1 is lowered dramatically to ~1/10 to 1/20 of NRSF/REST (13). These data suggest that other zinc finger domains, notably zinc finger domains 6–8, contribute to DNA binding (13). To study the contributions of these zinc finger domains to DNA binding, a point mutation was introduced into each in which the amino acid Cys was changed to Arg. It has previously been established that this mutation disrupts the conformation and function of Cys2-His2 type zinc finger domains (14). As expected introducing this mutation into zinc finger domains 6–8 together (Z6,7,8mut) decreased DNA binding to an undetectable level. Binding of the mutant could only be detected by adding higher concentrations of the nuclear extract. Similarly, combinations of mutations in any two of the three zinc finger domains (Z6,7mut, Z7,8mut, or Z6,8mut) greatly diminished binding to the NRSE/RE-1 probe. Single mutations in zinc finger domains 6 or 8 had little or no effect on
DNA binding; however, mutation of zinc finger domain 7 alone greatly reduced DNA binding. These data suggest that all three zinc finger domains can contribute to DNA binding; however, two adjacent zinc fingers, either zinc finger 6 plus 7 or zinc finger 7 plus 8, are required to produce maximal DNA binding. Although zinc finger domains 6–8 contribute to DNA bind-
ing, REST4, which lacks these domains as well as zinc finger domain 9, appears to be efficiently targeted to the nucleus (Figs. 3 and 4). REST4 also lacks the putative nuclear localization signal found in the C-terminal region of NRSF/REST (1, 16). Therefore, either there are two nuclear localization signals in NRSF/REST, or the nuclear localization signal found in REST4 is the functional one. Deletion mutagenesis previously indicated that the nuclear targeting signal of REST4 resides within the C-terminal region containing zinc finger domains 2–5 (15), and this was confirmed in this study by both cell fractionation and in vivo fluorescence measurements using GFP-REST4 constructs. We further demonstrated that zinc finger domains 2–5, but not 2–4, could target β-galactosidase to the nucleus. In addition, REST1, which is similar to REST4, but lacks zinc finger domain 5, was not targeted to the nucleus. Although these results would suggest that zinc finger 5 is required for nuclear localization, a point mutation in zinc finger 5 did not prevent nuclear localization. We can conclude that there is a nuclear targeting signal, other than the zinc finger domain, located within amino acids 296–328, which comprise the region preceding and through zinc finger 5. There are several basic residues in this region that could participate in a nuclear targeting signal. Alternatively, deletion of amino acids 296–328 changes the structure of the protein such that a critical conformation needed for nuclear targeting is disrupted.

To determine whether the zinc finger domain structures are important for nuclear targeting, REST4 with combinations of Cys to Arg point mutations in the zinc finger domains was constructed and fused C-terminally to GFP. None of the combinations of point mutations in zinc finger domains 2–5 changed the localization of REST4 from nuclear to cytoplasmic; thus, a functional structure of the zinc finger domains is not required to target REST4 to the nucleus. On the other hand, disruption of zinc finger domain 3 alone or in combination with other zinc finger domain mutations produced abnormal nuclear localization. A punctate staining of the nucleus was seen with the zinc finger domain 3 single mutant as well as with the zinc finger domain 3 and 4 and zinc finger domain 3 and 5 double mutants. These GFP-REST4 constructs appeared to enter the nucleus but were not dispersed uniformly throughout the nucleus. A different pattern was observed with the zinc finger domain 3 mutant in combination with a zinc finger domain 2 mutation. In these cases, the GFP-REST4 constructs appeared to localize to the edge of the nucleus, as if they were attached to the nuclear envelope.

It has been suggested that zinc finger domains not only function in DNA recognition (19), but also can be involved in protein-protein interactions (20, 21) and in determining subcellular localization (22, 23). Nuclear protein import including that of transcription factors such as NRSF/REST or REST4 is a key control point in regulating gene expression. Nuclear localization signal-mediated transport into the nucleus probably involves at least two processes: targeting to the nucleus and translocation with the nuclear pore complexes. The first step is suggested to be an energy-independent recognition of the targeting signal of the transport substrate and subsequent docking at the nuclear pore complexes. The second step is energy-dependent and involves translocation through the pore and into the nucleus (24, 25). Taken together, our results suggest the presence of three signals in REST4 that contribute to its nuclear localization. One signal, which does not require a functional zinc finger domain, is necessary to target REST4 to the nucleus. This signal lies within amino acids 296–328, since REST1 and the REST4 zinc finger 5 deletion mutant, both of which lack these amino acids, are not targeted to the nucleus. A second signal appears to be required to translocate REST4 across the nuclear membrane, and this signal appears to require both zinc finger domain 2 and zinc finger domain 3. Third, a signal residing in zinc finger domain 3 releases REST4 from the translocation machinery so that it can disperse throughout the nucleus. A less likely but alternative explanation is that the mutation in zinc finger domain 3 introduces a cryptic signal, which causes association of REST4 with nuclear membranes.

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