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Coiled-Coil Motif as a Structural Basis for the Interaction of HTLV Type 1 Tax with Cellular Cofactors

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ABSTRACT

Human T lymphotropic virus type 1 (HTLV-1) Tax is a multifunctional protein centrally involved in transcriptional regulation, cell cycle control, and viral transformation. The regulatory functions of Tax are thought to be mediated through protein–protein interaction with cellular cofactors. Previously we have identified several novel binding partners for Tax, including human mitotic checkpoint protein MAD1 (TXBP181), G-protein pathway suppressor GPS2 (TXBP31), and IκB kinase regulatory subunit IKK-γ. Here we described two additional Tax partners, TXBP151 and TXBP121. A closer examination of the sequences of eight independent cellular Tax-binding proteins identified by us and others revealed that all of them share a single characteristic, a highly structured coiled-coil domain. We also noted that Tax and the Tax-binding coiled-coil proteins can homodimerize. Additionally, the same domain in Tax is responsible for interaction with different coiled-coil proteins. Taken together, our findings point to a particular coiled-coil structure as one of the Tax-recognition motifs. The interaction of Tax with a particular subgroup of cellular coiled-coil proteins represents one mechanism by which Tax dysregulates cell growth and proliferation.

INTRODUCTION

HUMAN T LYMPHOTROPIC VIRUS TYPE 1 (HTLV-1) oncoprotein Tax is etiologically associated with adult T cell leukemia (ATL).[1] Tax is a 40-kDa nuclear phosphoprotein whose expression sufficiently immortalizes T lymphocytes[2–5] and transforms rat fibroblasts.[6,7] While the mechanisms for immortalization/transformation are incompletely understood, Tax has been shown to dysregulate cell cycle progression[8–10] and to subvert host DNA-damage and spindle-assembly checkpoints.[11–14] Tax is also a well-documented *trans*-activator of the HTLV-1 LTR as well as many cellular promoters[15] with abilities to activate CREB-, NF-κB-, and SRF-dependent transcription.[16–19]

Previously we have identified cellular proteins GPS2, MAD1, and IKK-γ as binding partners for Tax.[14,20–22] GPS2 binds Tax and is involved in Tax regulation of JNK1.[20] MAD1 is a novel mitotic checkpoint protein targeted by Tax. Tax interferes with cellular functions of MAD1 leading to abrogation of checkpoint. The Tax–MAD1 interaction provides a molecular explanation for karyotypic abnormalities seen in ATL cells.[14] The direct binding of IKK-γ to Tax serves an adapter function in Tax activation of NF-κB.[22] These and other findings[14,20–28] suggest that despite its pleiotropic effects, the specificity of Tax action occurs through protein–protein interaction with cellular cofactors. Thus, it would be of interest to better understand how Tax recognizes its cellular targets. Here we compared the sequences of Tax-binging proteins. Interestingly, a subgroup of at least eight Tax-binding proteins shares weak yet significant homology. Further analyses of the homologous sequences led to the identification of a highly structured coiled-coil domain as the recognition motif for Tax. We also provide evidence that these Tax-binding proteins dimerize. Moreover, using a series of Tax mutants we characterized the structural requirement of Tax for its interaction with these coiled-coil factors.

MATERIALS AND METHODS

Plasmids

Yeast expression vectors pAS2-1, pGBT9, pGAD424, and pACT2 are from CLONTECH. cDNAs coding for GPS2, IKK-γ, MAD1, TXBP151, Tax, and Tax mutants have been described elsewhere.[14,19,20–22,29] A partial TXBP121 clone was isolated from a HeLa S3 cDNA expression library (CLON-

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TECH). The full-length TXBP121/KIAA0445 cDNA[30] was a gift from Dr. Takahiro Nagase, Kazusa DNA Research Institute, Japan. Details for the plasmid constructs will be provided upon request.

Tax mutations are designated by the amino acid residue to be changed, the position of the residue, and the replacement residue (e.g., Tax C23-S).

Yeast two-hybrid analysis

Yeast two-hybrid analysis was performed as described.[29] A colony-lift filter assay was performed using 5-bromo-4-chloro-β-D-galactopyranoside (X-gal) as substrate. Results from the filter assay were verified by quantitative β-galactosidase assay based on chlorophenol red-β-D-galactopyranoside (CPRG).

Molecular sequence analysis[31–34]

Protein sequences were analyzed with the help of the Wisconsin package (version 10.0; Genetics Computer Group, Inc.). The COILS[35] and PAIRCOIL[36] algorithms were used for prediction of coiled-coil domains.

RESULTS

A subgroup of Tax-binding coiled-coil proteins

Previously we have identified Tax-binding proteins GPS2,[20] MAD1,[14] and IKK-γ.[21,22] We have further searched human cDNA libraries for additional Tax-binding cellular factors. Two novel Tax-binding proteins, TXBP151 and TXBP121, were identified, and we are now in the process of characterizing these proteins. Both have been verified as bona-fide Tax-binding proteins in independent interactive assays (coprecipitation, cofractionation, and colocalization).

We compared the amino acid sequences of GPS2, MAD1, IKK-γ, TXBP151, and TXBP121. Interestingly, all five Tax-binding proteins share distant sequence homology (10–20%), implying that there might be a common motif for recognition by Tax. Using the BLAST server (http://www.ncbi.nlm.nih.gov), we performed a homology search against all sequences in the extant databases. Several known coiled-coil proteins were identified in this search. Thus, INCENP (GenBank Z25420) is distantly related to GPS2 [smallest Poisson probability $P(N) = 4.7 \times 10^{-5}$]. Golgin-160 (Swissprot P55937) is related to MAD1 [$P(N) = 5 \times 10^{-16}$]. FIP2 (GenBank AF061034) is related to IKK-γ [$P(N) = 4 \times 10^{-15}$]. Myosin II heavy chain (GenBank U43192) is related to TXBP151 [$P(N) = 8 \times 10^{-17}$]. Cep250 (GenBank AF022655) is related to TXBP121 [$P(N) = 2 \times 10^{-40}$]. These homologies suggest that GPS2, MAD1, IKK-γ, TXBP151, and TXBP121 might be bona-fide coiled-coil proteins.

Indeed, computer analyses based on two different algorithms reveal that all five Tax-binding proteins harbor a coiled-coil domain (Fig. 1 and Table 1). Along this line of analysis, three Tax-binding proteins (CREB2/ATF4, TxBP1/hNF-66, and keratin 8/19) identified by us and others (Table 1) also contain coiled-coils. Together there are eight independent Tax-binding proteins that share a common characteristic, a highly structured coiled-coil domain. This suggests that a coiled-coil structure is

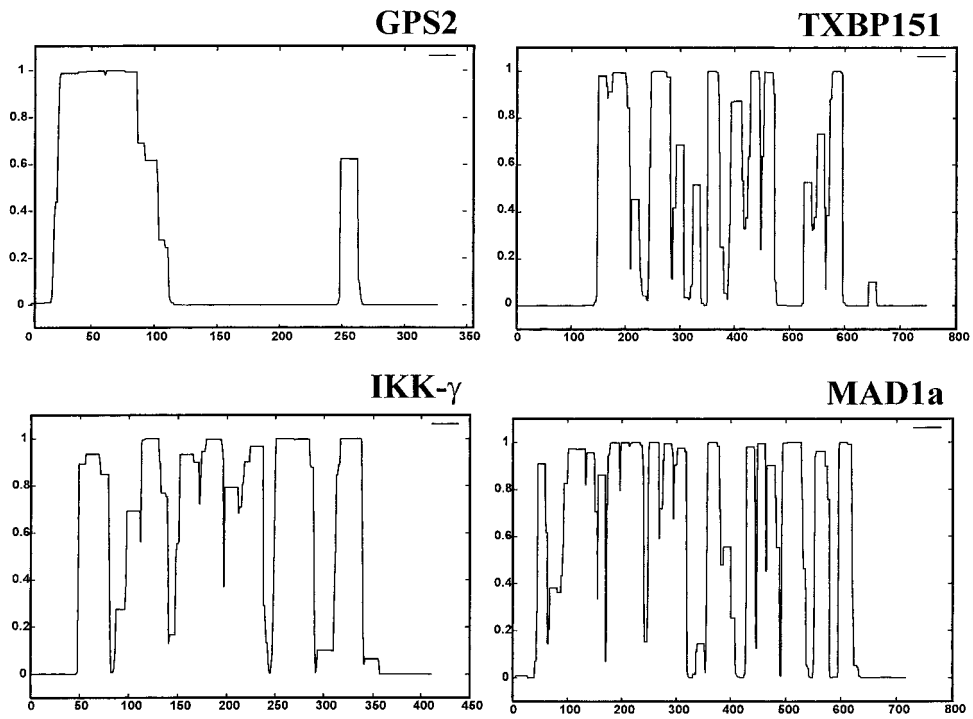

FIG. 1. Predicted coiled-coil structure in Tax-binding proteins GPS2, TXBP151, IKK-γ, and MAD1a. The *x*-axis represents residues in proteins. The *y*-axis is the probability of forming coiled coils. The plot was produced by the COILS program using the MTIDK matrix. Prediction by the PAIR–COIL program yielded similar readouts.

TABLE 1. TAX-BINDING PROTEINS WITH COILED-COIL DOMAINS

Tax-binding protein	*Coiled-coil domain*[a] *(aa)*	*Function*[b]	*References*
IKK-γ/NEMO	51–353	Regulatory subunit of IKK	21–24
GPS2/TXBP31	15–104	Suppressor of JNK activation	20
ATF4/CREB2	268–344	Transcriptional activator	25, 28
TXBP181/MAD1	50–630	Mitotic checkpoint protein	14, 45
TXBP151	150–600	Transcriptional activator	28, 46
TXBP121/KIAA0445	1–1280	Centrosomal protein	21, 30
TxBP-1/hNF-66	80–400	Neuronal specific IF protein	26
Keratin 8/19	80–400	Cytoskeletal protein	27

[a]Coiled-coil domain is predicted by the COILS program (http://www.ch.embnet.org).
[b]IF, intermediate filament.

a Tax-recognition motif. In agreement with this interpretation, the Tax-binding domains in GPS2, MAD1, TXBP151, and TXBP121 have been mapped to be within the respective coiled-coil region (unpublished data).

Dimerization of Tax-binding coiled-coil proteins

We and others have documented that Tax functions optimally as a homodimer.[29,37] Tax has also been shown to enhance dimerization of bZIP transcription factors leading to stimulation of DNA binding.[38–40] These findings have led us to propose a pleiotropic mechanism in which Tax facilitates the dimerization of its various binding partners.[29,41] In this regard, well-characterized Tax partners including CREB, NF-κB, and SRF function as dimers. Hence, we asked whether the Tax-binding coiled-coil proteins described here would also dimerize.

We used the yeast two-hybrid assay to assess for homo- or heterodimerization. Proteins fused to Gal4 DNA binding domain or Gal4 activation domain were tested reciprocally for binding in yeast cells (Table 2). We observed that Tax, GPS2, MAD1a, TXBP121, and TXBP151 indeed showed ability to self-associate. GPS2 was also found to complex with TXBP121. Thus, both Tax and Tax-binding coiled-coil proteins can homodimerize *in vivo*. Others have also verified by gel filtration and/or UV-crosslinking techniques that Tax and some Tax-binding proteins can dimerize.[37]

Definition of Tax domain for interaction with coiled-coil proteins

To map the structural domain within Tax responsible for interaction with the coiled-coil proteins, we tested 21 previously described Tax mutants for their ability to interact with GPS2, MAD1a, TXBP121, TXBP151, and IKK-γ (Table 3). These 21 mutants exhibited two binding phenotypes. Nine mutants, Tax Δ(3–6), Tax Δ(337–353), Tax C23–S, Tax S32–A, Tax H43–Q, Tax S113–A Tax S150–A, Tax L296–G, and Tax L320–G, bound to Tax and to each of our Tax-binding proteins equally well. In contrast, 12 other mutants [Tax Δ(3–10), Tax Δ(3–14), Tax Δ(2–58), Tax Δ(94–114), Tax Δ(94–103), Tax Δ(103–114), Tax Δ(284–353), Tax Q9–G, Tax C29–S, Tax C36–S, Tax H52–Q, and Tax S132–A] failed to bind Tax or any of the five Tax-binding proteins. Thus, while these results failed to reveal a single discrete linear subdomain in Tax that could explain binding, we noted that they suggest that a protein structure shared between wild-type and binding-competent Tax mutants account for both homodimerization and interaction with coiled-coil partners.

DISCUSSION

Here we show that eight Tax-binding proteins share a common finding of a highly structured coiled-coil domain (Table 1

TABLE 2. DIMERIZATION OF TAX AND TAX-BINDING PROTEINS[a]

	Tax	*GPS2*	*MAD1a*	*TXBP121*	*TXBP151*	*IKK-γ*
Tax	++	++	++	++	++	++
GPS2	++	++		++		
MAD1a	++		++			
TXBP121	++	++		++		
TXBP151	++				++	
IKK-γ	++					NA[b]

[a]The interaction between the two proteins was assayed by the yeast two-hybrid method. One of them was expressed as a Gal4 DNA-binding domain (Gal4BD) fusion protein, while the other was a Gal4 activation domain (Gal4AD) fusion. Strongly positive results in both qualitative filter assay and quantitative liquid assay are shown as ++.
[b]NA, not applicable (because Gal4BD–IKK-γ potently activates reporter expression).

TABLE 3. INTERACTION OF TAX MUTANTS WITH TAX-BINDING PROTEINS[a]

	Tax	*GPS2*	*MAD1a*	*TXBP121*	*TXBP151*	*IKK-γ*
Tax	++	++	++	++	++	++
Tax Δ(3–6)	++	++	++	++	++	++
Tax Δ(3–10)	−	−	−	−	−	−
Tax Δ(3–14)	−	−	−	−	−	−
Tax Δ(2–58)	−	−	−	−	−	−
Tax Δ(94–114)	−	−	−	−	−	−
Tax Δ(94–103)	−	−	−	−	−	−
Tax Δ(103–114)	−	−	−	−	−	−
Tax Δ(284–353)	−	−	−	−	−	−
Tax Δ(337–353)	++	++	++	++	++	++
Tax Q9–G	−	−	−	−	−	−
Tax C23–S	++	++	++	++	++	++
Tax C29–S	−	−	−	−	−	−
Tax S32–A	++	++	++	++	++	++
Tax C36–S	−	−	−	−	−	−
Tax H43–Q	++	++	++	++	++	++
Tax H52–Q	−	−	−	−	−	−
Tax S113–A	++	++	++	++	++	++
Tax S132–A	−	−	−	−	−	−
Tax S150–A	++	++	++	++	++	++
Tax L296–G	++	++	++	++	++	++
Tax L320–G	++	++	++	++	++	++

[a]The interaction between the two proteins was tested by the yeast two-hybrid assay. Tax or Tax mutants fused to Gal4BD were queried for interaction with the Gal4AD versions of Tax, GPS2, MAD1a, TXBP121, TXBP151, or IKK-γ. Reciprocally, Gal4BD versions of Tax, GPS2, MAD1a, TXBP121, and TXBP151 were queried for interaction with Gal4AD versions of Tax or Tax mutants. Please note that this is not applicable to Gal4BD–IKK-γ since it potently activates reporter expression in the absence of any Gal4AD fusion protein. Strongly positive results from both assays or from the assay with Gal4AD–IKK-γ are shown as ++. Negative results from both assays or from the assay with Gal4AD–IKK-γ are denoted as −.

and Fig. 1). These coiled-coil proteins can homodimerize (Table 2) and likely they all recognize the same structural domain within Tax (Table 3). We suggest that among cellular proteins a particular coiled-coil structure serves as a Tax recognition motif.

Coiled-coil proteins generally share 20–30% sequence homology with each other.[35,36] For these proteins, the relatively low degree of primary amino acid conservation is not reflected in apparently more significant similarities in secondary structures. The eight examples in Table 1 instructively suggest how Tax recognizes Tax-binding proteins. Based on these examples, Tax recognition is dictated more by secondary structure than by primary sequence. The fact that many other coiled-coil proteins do not bind Tax suggests further complexity to recognition specificity that remains to be elucidated. One notes that Tax and the Tax-binding proteins listed in Table 1 can all homodimerize (Table 2). In some cases (e.g., TXBP181/MAD1), it has been verified that the same coiled-coil structure is responsible for homodimerization and for binding to Tax.[14] In other cases, different coiled-coil subdomains serve for homodimerization and for Tax binding (e.g., TXBP151; unpublished data). Hence, homodimerization of Tax-binding proteins and their binding to Tax illustrate differential regulation through coiled-coil interactions.

Coiled coils are thought to be an evolutionarily conserved structure for protein–protein interaction.[35,36] Previously, PDZ proteins have been identified as a family of polypeptides that binds HTLV-1 Tax. In particular, a C-terminal domain within HTLV-1 Tax that is absent from HTLV-2 Tax was shown to bind to the PDZ domain.[42–44] Here the coiled-coil motif is shown to be another protein structure recognized by Tax.

Several Tax-binding coiled-coil proteins have been implicated in cell cycle control. MAD1a is a central component of the spindle assembly checkpoint.[14,45] TXBP151[46] is a nuclear transcriptional factor that regulates cell growth and proliferation. TXBP121 is a centrosomal protein involved in centrosome organization and duplication (unpublished data). Hence, further elucidation of the functional interactions of Tax with these coiled coil proteins is likely to yield biologically significant findings.

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