Tup1-Ssn6 Interacts with Multiple Class I Histone Deacetylases in Vivo*

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The Tup1-Ssn6 corepressor complex in *Saccharomyces cerevisiae* represses the transcription of a diverse set of genes. Chromatin is an important component of Tup1-Ssn6-mediated repression. Tup1 binds to underacylated histone tails and requires multiple histone deacetylases (HDACs) for its repressive functions. Here, we describe physical interactions of the corepressor complex with the class I HDACs Rpd3, Hos2, and Hos1. In contrast, no *in vivo* interaction was observed between Tup1-Ssn6 and Hda1, a class II HDAC. We demonstrate that Rpd3 interacts with both Tup1 and Ssn6. Rpd3 and Hos2 interact with Ssn6 independently of Tup1 via distinct tetratricopeptide domains within Ssn6, suggesting that these two HDACs may contact the corepressor at the same time.

The Tup1-Ssn6 corepressor complex mediates repression of a large and diverse set of genes in *Saccharomyces cerevisiae* (reviewed in Ref. 1). Examples of gene classes regulated by this co-repressor complex are genes that are repressed by glucose (e.g. *SUC2*), genes that respond to hypoxia (e.g. *ANB1*), genes induced by DNA damage (e.g. *RRN2*), and cell type-specific genes (e.g. *STE6*). Tup1-Ssn6 does not bind directly to DNA but is recruited to target genes by interactions with DNA-bound repressor proteins. The molecular mechanism by which Tup1-Ssn6 inhibits transcription is not fully understood, but Tup1-Ssn6 probably uses both interactions with chromatin and interactions with the general transcription machinery to achieve repression. Many subunits of the mediator complex that is associated with the C-terminal domain of the largest subunit of RNA polymerase II interact both genetically and physically with Tup1-Ssn6 (2–5).

Tup1-Ssn6 also directly interacts with histones and influences the organization of chromatin. Certain repressed genes under Tup1-Ssn6 control are packaged into highly positioned nucleosome domains during repression (6–9). Tup1 binds preferentially to underacylated H3 and H4 amino-terminal histone tails in *vitro*, and combined mutation of the H3 and H4 tails leads to a large derepression of Tup1-Ssn6-regulated genes *in vivo* (10, 11). Chromatin immunoprecipitation experiments indicate that Tup1 binding in *vitro* is associated with decreased acetylation of H3 and H4 (12–14). Accordingly, histone deacetylation activities are required for Tup1-Ssn6 repression (15, 16).

Combined loss of three class I histone deacetylases, Rpd3, Hos1, and Hos2, completely abolishes Tup1-Ssn6 repression at all genes examined (15). Mutations in the class II deacetylase, Hda1, shows partial derepression of *ENA1*, another Tup1-Ssn6-regulated gene (16). Interactions between Tup1-Ssn6 and Rpd3, Hos2, and Hda1 have been detected using a combination of *in vitro* and *in vivo* techniques. HA-Tup1 interacts with both a LexA-Ssn6 construct in *vitro* and a GST-Ssn6 construct in *vitro*. In *vitro* translated Hda1 interacts with GST-Tup1 in *vitro*. However, only Rpd3 has heretofore been shown to interact with native Tup1-Ssn6 *in vivo*.

In this work, we demonstrate that native Tup1-Ssn6 interacts with multiple class I HDACs *in vivo*. Moreover, we define independent HDAC interaction domains within the complex, suggesting that Tup1-Ssn6 may use several chromatin modifying activities to repress target genes.

**EXPERIMENTAL PROCEDURES**

*Strains—*HA-tagged alleles of Rpd3 and Hos2 were generously provided by D. Stillman (University of Utah) (15). Strain DY5329 contains the RPD3::3xHA LEU2 allele (a C-terminal HA tag), and strain DY5330 contains a HOS2::3xHA LEU2 (a C-terminal HA tag) allele. Hos1 and Hda1 were tagged in this laboratory by the method of B. Schneider et al. (17). Briefly, a cassette was generated by PCR that contained a 3xHA tag with URA3 flanked by direct repeats with end regions homologous to HOS1 or HDA1. Yeasts were transformed with these cassettes, plated on -Ura medium and screened by PCR for homologous integration at the desired site. Selected colonies were then plated on 5-fluoroorotic acid to select against the URA3 gene, leaving one copy of the direct repeat and the 3xHA tag. Alleles of HOS1 and HDA1 tagged at either the N terminus or the C terminus were constructed. The expression of HA-Hos1 in both strains was equivalent, and we chose to use the C-terminal 3xHA strain (JDY36) in experiments presented here. No expression was detected for HA-Hda1 with a C-terminal tag, but robust expression was observed for the N-terminal tag construct. Thus, the N-terminal 3xHA tagged strain was used for these experiments (JDY42). Kan' gene replacements (18) were used to create the *tup1::Kan' or ssn6::Kan'* alleles in DY5329, DY5330, JDY36, and JDY42.

**Immunoprecipitations**—For immunoprecipitations, 200 ml of cells were grown to an OD<sub>600</sub> of 1.0. Cells were washed once with H<sub>2</sub>O, resuspended in 8 ml of lysis buffer with protease inhibitors, and frozen dropwise into liquid nitrogen. Cell lysis buffer was composed of 25 mM Tris, pH 7.5, 125 mM NaCl, 5% glycerol, 15 mM MgCl<sub>2</sub>, 15 mM EGTA, and 0.1 to 0.01% Tween 20. The co-immunoprecipitation experiments with Hos1 (Fig. 1B) and Rpd3 (Fig. 2, A and B) used cell lysis buffer with 0.1% Tween 20. All other experiments were done with 0.01% Tween 20. The frozen pellets were then transferred to a coffee grinder with dry ice and ground (19). Alternatively, ~5 ml of liquid nitrogen was added to the frozen pellets and ground for 10 s. This step was repeated two additional times. After the powder was thawed and centrifuged, 1 ml of the clarified supernatant was used for each immunoprecipitation. To immunoprecipitate Tup1 or Ssn6, 10 μl of anti-Tup1 (this laboratory) or

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anti-Ssn6 (this laboratory) were prebound to 50 μl of a 50% solution of protein A-agarose beads that had been prewashed with cell lysis buffer as above. Following the prebinding, the beads were washed two times with cell lysis buffer and then used for immunoprecipitations that were performed overnight at 4 °C. For immunoprecipitations with anti-HA and anti-V5, 2 μl of anti-V5 (Invitrogen) or anti-HA (12CA5, 5 mg/ml; Roche Applied Science) were used. The antibodies were mixed with cell lysates overnight, and 20–50 μl of a 50% solution of prewashed protein A-agarose beads were then added and incubated for an additional 2 h. Beads were then collected and washed three times with cell lysis buffer before adding loading buffer, boiling, and loading supernatants on an 8% SDS-PAGE gel.

Immunoblots were blocked in 5% milk in TBST (10 mM Tris, pH 7.5, 150 mM NaCl, 0.1% Tween 20). The following dilutions of primary antibody were used in 5% milk in TBST: 1:5,000 for anti-Ssn6, 1:2,500 for anti-Tup1, 1:5,000 for anti-V5 and 1:5,000 for anti-HA. Immunoblots were incubated with horseradish peroxidase-conjugated secondary antibody (1:25,000 dilution in 5% milk in TBST; Amersham Biosciences) and developed with Super Signal (Pierce).

GST Pull-down Assays—GST fusion proteins were purified as in Mukai et al. Yeast whole cell extracts from DY3529 (HA-Rpd3) and DY5330 (HA-Hos2) were prepared as described above for immunoprecipitations. Extracts (250 μl) were incubated with purified GST fusion proteins bound to glutathione beads for 30 min at room temperature. The beads were then washed four times in extraction buffer and resuspended in SDS-PAGE loading buffer. The GST fusions used were GST-Tup1N (amino acid positions 7–253), GST-Tup1C (amino acid positions 253–713), GST-Ssn6N (amino acid positions 1–398), and GST-Ssn6C (amino acid positions 428–966).

RESULTS

To determine whether native Tup1-Ssn6 interacts with particular HDACs, we performed coimmunoprecipitation experiments. We obtained or constructed strains that contained an insertion of a 3X HA epitope at the endogenous locus of RPD3, HOS1, HOS2, or HDA1. Thus, the tagged proteins are expressed from their natural promoters (Fig. 1A). HA-Rpd3, HA-Hos2, and HA-Hda1 all show robust expression as detected by an immunoblot of cell extracts using an anti-HA antibody. Hos1 is not readily detectable in whole cell extracts but is visible on an immunoblot following immunoprecipitation (Fig. 1B). Insertion of the 3X HA tag at either the N terminus or C terminus of Hos1 showed equivalent low expression of HA-Hos1 (data not shown). HA-Hos1 expression, then, is significantly lower than that of the other HDACs.

We have shown previously that HA-Rpd3 co-immunoprecipitates with Tup1-Ssn6, so we looked for interactions between native Tup1-Ssn6 and other HDACs. Immunoprecipitations were performed with anti-HA, anti-Tup1, and anti-Ssn6. We find that both HA-Hos1 and HA-Hos2 immunoprecipitate with Tup1-Ssn6 (Fig. 1, B and C). Antibodies to the HA epitope immunoprecipitated HA-Hos1 and Tup1-Ssn6, as detected using anti-Ssn6 or anti-Tup1 antisera (Fig. 1B). We did not detect Hos1 in anti-Tup1 or anti-Ssn6 immunoprecipitates. Perhaps recognition of epitopes in Tup1 or Ssn6 by our antibodies to these native proteins interfered with interactions with this HDAC. Given the very low expression level of Hos1 (Fig. 1A), it is also possible that small amounts of Hos1 immunoprecipitated by anti-Tup1 or anti-Ssn6 antibodies would be below the limits of detection of these experiments. The anti-Ssn6 antibody was able to immunoprecipitate HA-Hos2 as well as Tup1 (Fig. 1C). Interestingly, no HA-Hos2 could be detected in anti-Tup1 immunoprecipitates (data not shown), and we were unable to detect Tup1 or Ssn6 in anti-HA immunoprecipitations for Hos2. As above, the ability to detect interactions in these coimmunoprecipitations may be limited by epitope blockage or by the transient nature of the interactions. Finally, we performed coimmunoprecipitation experiments using strains bearing HA-Hda1, but we were unable to detect any interactions between HA-Hda1 and Tup1-Ssn6 in vivo with any of the antibodies (data not shown).

Rpd3 and Hos2 Interact with Ssn6 Independently of Tup1—Next, we asked if Rpd3, Hos2, or Hos1 made contacts with Tup1, Ssn6, or both proteins in the corepressor complex. For these experiments, we disrupted TUP1 or SSN6 in the tagged HDAC stains. Interestingly, HA-Rpd3 interacts well with Ssn6 in the absence of Tup1 but can also interact, albeit more weakly, with Tup1 in the absence of Ssn6 (Fig. 2, A and B). Thus, it appears that HA-Rpd3 contacts both Ssn6 and Tup1. HA-Hos2 also interacted well with Ssn6 in the absence of Tup1 (Fig. 2C). However, since anti-Tup1 does not co-immunoprecipitate HA-Hos2, we could not address whether Tup1 interacts independently with HA-Hos2. For HA-Hos1, we were unable to detect an interaction in the absence of either Tup1 or Ssn6, suggesting that Hos1 requires both proteins to contact the complex (data not shown). The very low expression level of Hos1, however, confounded these studies, so we did not further map HA-Hos1 interactions with the corepressor.

Rpd3 and Hos2 Interact with the N Terminus of Ssn6 in Vivo—To begin mapping the domains of Tup1 and Ssn6 that interact with HA-Rpd3 and HA-Hos2, we performed a GST pull-down experiment (Fig. 3). GST fusions with C-terminal or N-terminal portions of Ssn6 and Tup1 were incubated with extracts from strains bearing HA-Rpd3 or HA-Hos2. HA-Rpd3 interacts with the N terminus of Ssn6 (GST-Ssn6N) and the C terminus of Tup1 (GST-Tup1C). HA-Hos2 interacts with the N terminus of Ssn6 and shows no interaction with the N- or C-terminal regions of Tup1. We observed no binding of HA-Rpd3 or HA-Hos2 to GST alone (data not shown).
Rpd3 and Hos2 Interact with the TPR Domain of Ssn6—Since both HA-Hos2 and HA-Rpd3 interact with the N terminus of Ssn6, we mapped the domains of Ssn6 that interact with these HDACs. The N terminus of Ssn6 contains 10 TPR repeats, a protein-protein interaction motif. This region has been shown previously to contact DNA-bound repressor proteins. Moreover, Tzamarias and Struhl (20) showed that different classes of Tup1-Ssn6-regulated genes require different TPR domains for repression. We patterned our clones after those used in these earlier studies (20). Our constructs contain a V5 epitope on the C terminus and are under the control of the GAL1 promoter. A diagram of these V5-Ssn6 fusion clones and their expression levels in galactose is shown in Fig. 4. To avoid interference from native Ssn6, these experiments were all done in ssn6Δ strains. HA-tagged HDACs coimmunoprecipitated by anti-V5 antiserum were detected with anti-HA immunoblots (Fig. 5).

HA-Rpd3 interacts with the TPR domain of Ssn6, and this interaction appears to require the entire TPR domain (Fig. 5A). HA-Rpd3 did not interact with any construct deleted for any of the TPR repeats. HA-Hos2 also interacted with the TPR domain, but, in contrast to HA-Rpd3, HA-Hos2 interacted quite well with a construct that only contains TPRs 2–7 (Fig. 5B). Thus, HA-Hos2 does not require TPR 1, 8, 9, or 10 for interaction. Interestingly, the construct that contains only TPRs 2–7 deletes the Tup1 interaction domain, consistent with our finding above that Tup1 is not required for Hos2 interactions with Ssn6. Similar experiments under these conditions were also done using strains expressing HA-Hda1 (Fig. 5C). No interaction was observed between HA-Hda1 and any Ssn6 construct, consistent with the lack of coimmunoprecipitation of HA-Hda1 with the native Tup1-Ssn6 complex. We did note that expression of HA-Hda1 was lowered in Δssn6 cells, but sufficient levels of HA-Hda1 were present in the cell to allow detection of an interaction had one occurred under these conditions (see extract lane, Fig. 5C).

**DISCUSSION**

Tup1-Ssn6 utilizes histone deacetylases and histone contacts to mediate repression. The details of this repression mechanism are not understood but are fundamental to understanding corepressor functions. We have shown previously that simultaneous loss of RPD3, HOS1, and HOS2 leads to complete derepression of Tup1-Ssn6-regulated genes (15). This mutant combination also increases the acetylation at Tup1-Ssn6-regulated genes (15) and severely inhibits the cross-linking of Tup1 to target genes (14). Each individual HDAC mutation has only minor effects on repression. The greater effects of the combined HDAC mutations might reflect overlaps in the substrate specificities of these enzymes. Alternatively, they might reflect the ability of the corepressor to interact with and utilize multiple chromatin remodeling activities to tailor gene-specific repressive architectures. In support of this idea, we demonstrate here that each of the class I HDACs genetically determined to be important for Tup1-Ssn6 functions interacts with native Tup1-Ssn6 in vivo.

In previous studies, we also observed a modest degree of derepression of an a cell-specific reporter gene in hda1 mutant cells (21), consistent with the findings of Wu et al. (16) that indicate Hda1 is important to some Tup1-Ssn6 functions. However, the effects of HDA1 mutation on repression of the reporter gene, endogenous a cell-specific genes, or SUC2 were much smaller than those of the combined mutations in RPD3, HOS1, and HOS2 (15, 21). Furthermore, no greater loss of repression was observed upon combination of HDA1 mutations with mutations in other HDACs, in contrast to the synergistic effects of RPD3, HOS1, and HOS2 mutations on repression. These results indicate that Hda1 is less important than the class I HDACs in the repression of a cell-specific genes or SUC2. Hda1 may play a more dominant role in repression of other Tup1-Ssn6 target genes, such as ENA1 or genes located in the HAST (Hda1-associated subtelomeric) domains defined by the Grunstein laboratory (16, 22). Indeed, at ENA1, a similar pattern of changes in histone deacetylation is observed in hda1Δ cells and tup1Δ cells (16). Whereas in vitro translated Hda1 interacts with GST-Tup1 in vitro (16), we do not detect any interaction between this HDAC and the corepressor in vivo, implying that such an interaction might be much more transient than interactions between Tup1-Ssn6 and the class I HDACs.
In contrast, our data demonstrate that Rpd3 and Hos2 interact strongly with Tup1-Ssn6 in vivo. Interestingly, Wu et al. (16) observed increased histone acetylation in the coding region of *ENA1* in *rpd3/H9004* cells, whereas increased acetylation was observed in the *ENA1* promoter region in *tup1/H9004* cells and *hda1/H9004* cells. Since Tup1-Ssn6 is probably recruited to the promoter region of this gene to initiate repression, these data again suggest a link between Tup1-Ssn6 functions and Hda1 at this gene. Different patterns of changes in histone deacetylation have been observed at different Tup1-Ssn6 targets (13, 15, 16), suggesting that the corepressor may utilize different combinations of activities to repress different genes and that the effects of the corepressor may reach beyond the promoter region in some cases (14, 23).

The interactions we observe between Hos2 and Tup1-Ssn6 are particularly interesting, because Hos2 functions are correlated with transcriptional activation (24). Genome-wide location studies indicate that Hos2 cross-links to the coding regions of active genes (24). These results are somewhat counterintuitive, since HDAC functions and decreases in histone acetylation are usually correlated with gene repression. Of course, deacetylation of a particular histone at a specific site might facilitate transcription, or Hos2-mediated deacetylation of a nonhistone target may be important to gene activation. In either case, interaction of Tup1-Ssn6 with Hos2 might interfere with such functions to inhibit gene expression. However, Tup1-Ssn6 participates in the activation of some genes (25, 26), raising the possibility that Ssn6-Hos2 interactions might stimulate rather than inhibit transcription at these targets. Whereas Tup1 is highly enriched at the promoter regions of genes such as *RNR2* and *STE6* only under conditions of repression (14, 16, 23), Tup1 is enriched at promoter sequences of *SUC2* and *GRE2* under conditions of both activation and repression (25, 26). At *GRE2*, Tup1 is required for the recruitment of Swi/Snf and SAGA during activation (26), indicating that it plays a direct role in activation of this gene. Additional studies are needed to determine whether Hos2 or other HDACs co-localize with Tup1 at these genes and, if so, how the interactions impact expression of these genes.

Hos2 is part of a complex that contains Set3, a putative methyltransferase (27). The Set3 complex also contains Hst1, an NAD-dependent deacetylase, and Sif2, a WD repeat protein. At present, we do not know if Tup1-Ssn6 interacts with this complex or with Hos2 alone. Interestingly, the Set3 complex is suggested to be the *S. cerevisiae* homolog of SMRT and N-CoR (27). SMRT-N-CoR complexes also contain WD repeat proteins, TBL and TBLR1. Like Tup1, the TBL proteins interact with histones (28). N-CoR and SMRT contain numerous repression domains and have been reported to interact with the mSin3A-HDAC1/2 complex as well as HDACs 3–7 (29–32). However, when N-CoR or SMRT complexes are biochemically purified, the only histone deacetylase stably associated with the complex is HDAC3, a class I HDAC (33–35). HDAC4, a class II HDAC, also associates with the complex, but mutations in the HDAC4...
catalytic site do not affect the HDAC activity of the complex, whereas mutations in HDAC3 abolish the activity of the complex (36). These data indicate either that HDAC4 is not active in the complex or that HDAC3 is required to activate HDAC4. It will be interesting to determine whether isolated Tup1-Ssn6 complexes purified from yeast are associated with both class I and class II HDACs and, if so, whether both are active in the context of this corepressor. Dissecting the nature of Tup1-Ssn6-HDAC interactions in vitro and understanding how Tup1-Ssn6 utilizes specific HDACs to repress target genes in vitro will greatly increase our understanding of corepressor functions.

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