Histone deacetylase-associating Atrophin proteins are nuclear receptor corepressors

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Drosophila Tailless (Tll) is an orphan nuclear receptor involved in embryonic segmentation and neurogenesis. Although Tll exerts potent transcriptional repressive effects, the underlying molecular mechanisms have not been determined. Using the established regulation of knirps by tll as a paradigm, we report that repression of knirps by Tll involves Atrophin, which is related to vertebrate Atrophin-1 and Atrophin-2. Atrophin interacts with Tll physically and genetically, and both proteins localize to the same knirps promoter region. Because Atrophin proteins interact with additional nuclear receptors and Atrophin-2 selectively binds histone deacetylase 1/2 (HDAC1/2) through its ELM2 (EGL-27 and tors and Atrophin-2 selectively binds histone deacetylase 1/2 (HDAC1/2) through its ELM2 (EGL-27 and Atrophin-2) domains, our study establishes that Atrophin proteins represent a novel class of nuclear receptor corepressors.

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Nuclear receptors (NRs) comprise one of the largest known families of eukaryotic transcription factors (Mangelsdorf and Evans 1995). The majority of identified NRs are “orphans,” without known ligands. Many of these orphan NRs are conserved between vertebrates and flies (King-Jones and Thummel 2005), which makes the fly an ideal model system to study their properties. A major function of NRs is transcriptional repression. For unliganded members of subfamily 1 of the NR superfamily (NR1), such as thyroid hormone receptor (TR), retinoic acid receptor (RAR), and ecdysone receptor (EcR), their repression is often mediated by corepressors from the SMRT/N-CoR/SMRTER family (Chen and Evans 1995; Horlein et al. 1995; Tsai et al. 1999; Privalsky 2004; Tsai and Fendell 2004), which share a conserved SANT (SWI3/ADA2/N-CoR/TFII-B) domain (Aasland et al. 1996) and a repeated arginine–glutamic acid (RERE) stretch (Tsai et al. 1999). The conservation of the SANT domain, which is present in several other chromatin and transcriptional regulators (Aasland et al. 1996), and of the RERE stretch in SMRT/N-CoR/SMRTER suggests that these two domains are functionally significant. The SANT domain appears to enable various transcriptional regulators to carry out different chromatin-modifying tasks in a context–dependent manner. For example, (1) a SANT domain of ADA2 and SMRT interacts with histone tails (Boyer et al. 2002; Yu et al. 2003); (2) a SANT domain of SMRT binds to and activates histone deacetylase 3 (HDAC3) (Guenther et al. 2001; Yu et al. 2003; Codina et al. 2005); and (3) a SANT domain enables CoREST, a corepressor of REST, to stimulate histone demethylation activity for LSD1 (Shi et al. 2005). Tailless (Tll) is an orphan NR2 protein first identified as a terminal gap gene product involved in Drosophila segmentation (Pignoni et al. 1990). Tll is expressed at both anterior and posterior poles of the embryo. It strongly represses the transcription of another gap gene, knirps (kni) (Pankraz et al. 1989). Similar repression of kni can be achieved by Tlx, the vertebrate cognate of Tll, when it is ectopically expressed in Drosophila embryos (Yu et al. 1994). The similar transcriptional properties of Tll and Tlx imply that both proteins recruit similar corepressor[s] to repress kni in Drosophila. Thus far, no strong candidates for corepressors of Tll/Tlx have been identified.

In this study, we report the identification of Atrophin (Atro; also known as Grunge), which encodes a SANT domain, a RERE stretch, and an ELM2 (EGL-27 and MTA1 homology 2) domain, as an interacting factor of Tll. Mutations of Atro have been shown to cause a variety of patterning defects in Drosophila (Erkner et al. 2002; Zhang et al. 2002; Fanto et al. 2003; Kankel et al. 2004); because Atro is related to two vertebrate proteins, Atrophin-1 [Atr1], a dentatorubral pallidoluysian atrophy (DRPLA) protein (Koida et al. 1994; Nagafuchi et al. 1994), and Atrophin-2 [Atr2], also called RERE (Yanagisawa et al. 2000; Waermer et al. 2001), we further investigated the relationships between Atro proteins, nuclear receptors in both Drosophila and vertebrate cells. Our study reveals that Atro proteins represent a new class of nuclear receptor corepressors, whose ELM2 and SANT domains play a central role in mediating their HDAC activity.

Results and Discussion

Identifying Atro as a Tll-interacting factor

Since SMRT is a transcriptional corepressor for many NRs (Privalsky 2004) and SMRTER is the Drosophila cognate of SMRT (Tsai et al. 1999), our first step in identifying Tll/Tlx-interacting corepressors was to test whether Tll and Tlx interact with SMRT and SMRTER. Using yeast two-hybrid assays, we found that, whereas EcR, TR, and RAR interact with both SMRTER and SMRT, both Tll and Tlx fail to interact with SMRTER or SMRT [Supplementary Fig. 1].

To find potential corepressors of Tll/Tlx, we turned to a yeast two-hybrid screen, in which a Tll-expressing bait construct was deployed against a Drosophila embryonic library. A positive clone was identified, whose insert codes for the [1301–1966] region of Atro. This clone was
selected for further investigation for several reasons: [1] In yeast, this clone also interacts strongly with chick and human Tlx, but not with RAR or TR (Fig. 1A); [2] Atro encodes a SANT domain, a RERE stretch, and an ELM2 domain; [3] Atro is a transcriptional co-repressor of the Drosophila segmentation gene even-skipped [Zhang et al. 2002]; [4] two Atro-related proteins, Atr1 and Atr2, exist in vertebrates [Koide et al. 1994; Nagafuchi et al. 1994; Yanagisawa et al. 2000, Waerner et al. 2001]; and [5] Atr2 interacts with HDAC1 in mouse embryos [Zoltewicz et al. 2004]. These properties of Atro proteins highlight the possibility that they are corepressors for Tll and Tlx.

**LBD is required for Tll/Tlx to interact with Atro**

To determine which region in Tll is required for Atro association, we generated the series of truncated Tll expression constructs shown in Figure 1B and tested their interactions with Atro in yeast. The (192–452) region of Tll was found to be sufficient to mediate its interaction with Atro. Since this region of Tll harbors its ligand-binding domain (LBD), this suggested to us that an intact LBD is required for Tll to bind Atro. Indeed, no association between Tll variants lacking an intact LBD [e.g., Tll(33–161) or Tll(132–352)] and Atro could be detected.

A LBD-dependent interaction between Tll and Atro was further confirmed in human cells by using an immunostaining approach. CFP-tagged Atro (CFP-Atro) localizes to subnuclear regions when expressed in cells (Fig. 1C). This nuclear focal pattern of Atro resembles the nuclear pattern known for Atr2 [Yanagisawa et al. 2000, Waerner et al. 2001]. Expressing Atro with Tll or Tlx in the same cells alters the nuclear distribution of Tll and Tlx: Both Tll and Tlx shift from their evenly distributed nuclear patterns [Supplementary Fig. 2] to punctate nuclear patterns virtually identical to that displayed by CFP-Atro. Deleting the LBD from Tll and Tlx abrogates their localization to Atro-positive nuclear foci, confirming that Atro–Tll/Tlx interactions are mediated through the LBD of Tll and Tlx.

We next mapped the regions in Atro responsible for Tll or Tlx interaction, using the serial deletion Atro constructs shown in Figure 1D. Two regions in Atro were found to mediate its interaction with Tll: Tlx(956–1511) interacts weakly with Tll, whereas Atro(1711–1966) interacts strongly with both Tll and Tlx. The latter finding is of great interest, since the 1711–1966 region of Atro contains sequences conserved in the C-terminal regions of vertebrate Atr1 and Atr2. This correlation prompted us to investigate whether Atr1 and Atr2 interact with Tll or Tlx.

**Interactions between Atro and Tll/Tlx depend on a conserved Atro-box**

Accordingly, two constructs expressing the C-terminal regions of Atr1 and Atr2 were generated and tested individually against Tll- or Tlx-expressing plasmids. As expected, both Atr1(846–1191) and Atr2(1224–1566), like Atro(1711–1966), interact strongly with Tll and Tlx. The latter findings are of great interest, since the 1711–1966 region of Atro contains sequences conserved in the C-terminal regions of vertebrate Atr1 and Atr2. This correlation prompted us to investigate whether Atr1 and Atr2 interact with Tll or Tlx.

**Atro proteins interact with additional nuclear receptors**

Tll/Tlx belong to the NR2 subfamily of the NR superfamily. The similarity shared by members of the NR2 subfamily suggests that additional NR2 proteins may interact with Atro proteins as well. We tested this possibility first with GST pull-down assays, in which several as35-methionine-labeled NR2 and NR1 proteins were tested for their interactions with GST or GST-Atro fusion proteins. As shown in Figure 2D, Atro proteins specifically bind Tll, Tlx, human chicken ovalbumin upstream promoter-transcription factor (COUP-TF), and Seven-Up1 (SVP1) [the Drosophila COUP-TF homolog], but not TRβ and Ultraspiracle (USP). A similar interacting profile was observed between Atro proteins and COUP-TF or SVP1 in yeast [Supplementary Fig. 3].
in the P-element excision line, the embryos (Fig. 3A). Removal of zygotic Atro maternal and zygotic maternal deposition Atro. When maternal alone or both does not cause such expansion, due to the presence of electrophoresis. 

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, and USP. The bound proteins were resolved by gel \( n + 1 \) units (mean \( + SD, n = 3 \)). \( D \) GST pull-down assays showing the preferential binding of Atro proteins to NR2 proteins. Bacterially expressed GST or GST fusion proteins were mixed with in vitro translated \( 3^{35} \)-methionine-labeled NRs, including Tll, hTlx, COUP-TF, SVP1, TRB, and USP. The bound proteins were resolved by gel electrophoresis.

Therefore, Atro proteins do not interact with all NRs; rather, they preferentially bind a subset of NR2, including Tll, hTlx, COUP-TF, SVP1, TRB, and USP. The bound proteins were resolved by gel electrophoresis.

**Atro and tll interact genetically to repress kni expression in Drosophila**

Having demonstrated that Atro physically interacts with various NRs, we turned to the biological relevance of these interactions. In this study, we focus on the in vivo relationship between Atro and Tll in flies by exploiting the known role of Tll in the segmentation process during Drosophila early embryogenesis. At this stage, Atro is expressed as a nuclear protein throughout the embryos (Erkner et al. 2002, Zhang et al. 2002). Consistent with previous observations that tll represses kni expression at the posterior end of the embryo (Pankratz et al. 1989), in situ hybridization for kni expression expands posteriorly in early embryos, mimicking that found in tll embryos (note that tll is a deficiency line, in which the tll gene unit is removed. Accordingly, we generated a tll, Atro double-mutant fly line, in which both tll and Atro alleles were recombined to the same chromosome, and tested kni expression in the resulting homozygous mutant embryos. Indeed, a further posterior expansion of kni stripe was observed in tll, Atro double-mutant embryos, mimicking that found in tll embryos (note that tll is a deficiency line, in which the tll gene unit is

**Figure 3.** Atro and tll act together to repress kni. \( A \) In situ hybridization experiments showing the expression patterns of kni in each of the indicated mutant embryos. \( 1^{-} \) or \( m^{-} \) indicates that only the zygotic or the maternal contribution of Atro is depleted; \( m + z^{-} \) indicates that both maternal and zygotic Atro are depleted. tll is a hypomorphic allele; tll is a deficiency line; Atro is a P-element excision line; tll, Atro is a double-mutant fly line. The posterior margin of each kni stripe on the ventral side of the embryo is marked with an arrowhead. The enlarged image on the right corresponds to the posterior-ventral region of the embryo on the left. All embryos are shown with their anterior to the left and dorsal side up. Bar, 30 \( \mu M \). \( B \) In situ hybridization experiments showing the expression patterns of ftz in each of the indicated embryos. The pair-rule stripes of ftz from anterior to posterior are labeled from 1 to 7. \( C \) Schematic diagram showing the kni gene locus and two regions targeted for ChIP assays. The two tested regions are labeled P1 and P2. A Tll-binding site (in red) and its flanking sequences in P1 are shown. \( D \) ChIP assays showing the specific binding of Atro and Tll to the P1 region in the kni promoter. Assays were performed on 0- to 4-h-old wild-type embryos with the indicated antibodies or IgG. CG11562 is a randomly chosen gene whose promoter was used as a negative control. In “mock” experiments, no chromatin was added.
entirely deleted. We therefore conclude that Atro is required for Tll to repress kni.

Since Atro is a binding factor of another terminal gap gene product, Huckebein (Hkb) (Zhang et al. 2002), we additionally examined the expression of kni in hhβ mutant embryos. No significant posterior expansion of kni was observed, therefore indicating that the repression of kni in the posterior-terminal region primarily results from the combined effect of Tll and Atro.

The genetic interaction between tll and Atro was further assessed by monitoring the expression of the pair rule gene fushi tarazu (ftz) in the posterior region of the mutant embryos discussed above. In wild-type and in Atro35 zygotic mutant embryos, ftz is expressed as seven stripes in the central region (Fig. 3B). In tll' embryos, however, the posterior stripes of ftz (mostly the fifth, sixth, and seventh stripes) shift toward the posterior end. In the most severely affected tll' embryos, the seventh stripe of ftz is lost. This altered ftz pattern is known to be the consequence of cell fate changes, partly owing to the posterior expansion of kni, when tll is mutated (Mann and Lengyel 1987). In tll', Atro35 double-mutant embryos and in tll' embryos, additional loss of the sixth stripe of ftz was observed. Because the cell fate change is more pronounced in tll', Atro35 double mutants than in tll' Atro35 mutant embryos, we conclude that Atro participates with Tll in determining posterior-terminal cell fates in early Drosophila embryos.

Atro is recruited to the kni promoter

To verify the involvement of Atro in the regulation of kni by Tll at the chromatin level, we carried out chromatin immunoprecipitation (ChIP) assays for 0- to 4-h-old Drosophila embryos using Atro antibody, Tll antibody, and control IgG, respectively. The immunoprecipitated (IP) chromatin was subjected to PCR using primers corresponding to two separate regions, P1 and P2, in the kni gene (Fig. 3C), and a region in a randomly selected gene (CG11562) promoter. In the kni promoter, P1 resides 2.5 kb upstream of the transcription initiation site and has a defined Tll-binding site (Pankratz et al. 1992). P2 corresponds to the 3' untranslated region of the kni gene, where no Tll-binding site is found.

Our in vivo ChIP assays revealed that both Atro and Tll antibodies, but not the control IgG, specifically precipitated chromatin that harbors the P1 site, but not chromatin containing P2 or the CG11562 promoter (Fig. 3D). These results establish that Atro, by forming protein complexes with Tll, is present naturally on the kni promoter.

Atro and Atr2, but not Atr1, exert potent HDAC activities

Many transcriptional corepressors, including SMRT and N-CoR, are associated with HDAC activity. Because our results indicate that Atro proteins are corepressors of Tll/Tlx, we further investigated (1) whether Atro proteins also show HDAC activity, (2) whether Atro proteins bind selected HDACs, and, if so, (3) which regions/domains in Atro proteins mediate their HDAC binding. To address these interconnected questions, fluorometric HDAC assays and Western blot analysis were performed on protein complexes immunoprecipitated by Flag-tagged Atro, Atr1, Atr2, or truncated Atr2 variants expressed in HEK293 cells. In parallel experiments, Flag and Flag-SMRT were used as a negative and a positive control, respectively. The expression of tested Flag fusion proteins was first examined using Western blot analysis (Fig. 4A, right panel).

As expected, Flag-SMRT is associated with potent HDAC activity that is sensitive to trichostatin A (TSA), an HDAC inhibitor (Fig. 4B). Robust levels of TSA-sensitive HDAC activity were also observed for both Atro and Atr2, confirming that both proteins’ properties involve HDACs. To our surprise, Atr1 displays no prominent HDAC activity. Since Atr1 lacks the conserved ELM2 and SANT domains found in the N-terminal regions of Atr2 and Atro, we suspected that the missing N-terminal region in Atr1 might be important for the HDAC activity of Atro proteins.

ELM2/SANT domains mediate HDAC activity and HDAC1/2 association

To determine whether the HDAC activity of Atro or Atr2 depends on its N-terminal region, the BAH (Bromo adjacent homology), the ELM2, and the SANT domains in this region of Atr2 were deleted sequentially (Fig. 4A, lanes 5–7). Note that the BAH domain is absent in Atr2. Whereas Atr2ΔBAH still exerts a robust level of HDAC activity, a dramatic reduction of HDAC activity was ob-

**Figure 4.** The ELM2/SANT domains mediate HDAC activity and HDAC1/2 association. (A) Diagram showing the Flag-tagged proteins used in the HDAC assays and coimmunoprecipitation experiments. The functional domains in Atro proteins and the SNOR (SMRTER/SMRT/N-CoR) domain in SMRT are labeled with different colors. The Flag tag is shown as a gray box. The expression of proteins used for both assays is shown on the right. (B) Chart showing the HDAC activity associated with each tested Flag fusion protein corresponding to those shown in A. TSA was used at the concentration of 1 μM. (NE) HeLa nuclear extracts; (NC) negative control (solutions without input protein). (C) Western blot analysis showing the preferential binding of Atro and Atr2 to HDAC1 and HDAC2. IP protein complexes associated with each Flag fusion protein were probed with the indicated antibodies. (WCE) Whole-cell extracts; (IP) immunoprecipitated proteins.
served with Atro2ΔBAH-ELM2 [Fig. 4B]. A further deletion of the SANT domain, Atro2ΔBAH-ELM2-SANT, causes a complete loss of HDAC activity, indicating that both the ELM2 and SANT domains are central to Atro2’s HDAC activity.

We next investigated which HDACs Atro proteins interact with, and whether Atro2’s association with HDACs involves its ELM2/SANT domains. Protein complexes immunoprecipitated by Flag-tagged Atro proteins and Atro2 variants were examined by Western blot for a panel of potential associating proteins, including HDAC1, HDAC2, HDAC3, and Sin3A [Fig. 4C]. Sin3A was not detected in any of the IP complexes. In contrast, a significant level of HDAC3 was precipitated along with SMRT, which is in agreement with previous reports [Guenther et al. 2000; Li et al. 2000]. Although SMRT also interacts with HDAC1 or HDAC2, these interactions are considerably weaker. Conversely, abundant HDAC1 and HDAC2 [but only minimal HDAC3] are present in the protein complexes associated with Atro2. Similarly, Atro, but not Atr1, also precipitates HDAC1/2 specifically, indicating that Atro-family [except Atr1] and SMRT-family proteins display distinct preferences for different HDACs.

Consistent with our HDAC assay results [Fig. 4B], removing the ELM2 domain or both the ELM2 and SANT domains from Atro2ΔBAH impairs or disrupts its ability to associate with HDAC1/2 [Fig. 4C, lanes 6,7]. Given the fact that similar results were also obtained when we examined the distribution of endogenous HDAC1 in cells expressing different CFP-Atro2 variants [Supplementary Fig. 4], we therefore conclude that the ability of Atro2 to exert HDAC activity and to recruit HDAC1/2 depends on its ELM2 and SANT domains.

Prospects and implications

In many respects, the transcriptional properties that we discover here for Atro proteins parallel those found for SMRT, N-CoR, and SMRTER. As shown in Figure 5, [1] these two classes of corepressors share a SANT domain and RERE stretch; [2] they are conserved in vertebrates and in flies; [3] they bind NRs, albeit selectively; and [4] they associate with HDACs, also selectively. Additionally, Atr1, like SMRT and N-CoR, also interacts with ETO/MTG8 [Gelmetti et al. 1998; Wood et al. 2000], which is known to be a transcriptional repressor in human diseases, it is known that polyglutamine expansion in human Atr1 causes DRPLA [Koide et al. 1994; Nagafuchi et al. 1994]. We have shown that Atr1 lacks HDAC activity, yet it binds Atr2 through their RERE stretches [Yanagisawa et al. 2000], and it associates with both Tlx and COUP-TF, two known NRs with key roles in CNS development and functioning [Park et al. 2003; Roy et al. 2004; Shi et al. 2004]. We therefore propose that mutant Atr1 may cause its pathologic effects by interfering with the normal transcriptional properties of Atr2 and its associated nuclear receptors.

Materials and methods

Antibodies

Polyclonal Atro antibodies were developed in guinea pigs using KLH-conjugated synthetic polypeptides, ADTPALRQLSERPHVA, which correspond to the 1815–1832 region of Atro. For all our experiments, we used affinity-purified Atro antibodies. The sources of other antibodies are anti-Tailless [gift of J. Reinitz, State University of New York-Stony Brook, New York], anti-Flag [Sigma F-7425; 1:400], anti-HDAC1 [Upstate 06-720, 1:500], anti-HDAC2 (Santa Cruz 7899, 1:400), anti-HDAC3 (Santa Cruz 11417, 1:150), anti-Sin3A (Santa Cruz 767, 1:300), Texas-Red conjugated anti-rabbit [Jackson ImmunoResearch 711-075-152; 1:400], and anti-Digoxigenin [Roche, 1333089; 1:1500]. Immunofluorescence and microscopic analysis are described in Tsai et al. [2004].

Drosophila stocks and experiments

The til2, tll, and hkb2 lines were obtained from the Bloomington Stock Center. The Atro2 line is a gift of S. Kerridge (Center CNRS-INSERM-Université de la Méditerranée-AP de Marseille, France). Details for using the DFS-FLP method to generate Atro2 germline clones are described in Erkner et al. [2002]. The til2, Atro2 double-mutant line was generated by chromosomal recombination. All genetic experiments were carried out at 23°C. In situ hybridization experiments and the methods used to generate kini and fts RNA probes are described in Tsai and Gergen [1994].

Cell culture, transfection, and coimmunoprecipitation experiments are described in Mizutani et al. [2005]. Additional materials and methods are included in the Supplemental Material.

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