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In both invertebrates and vertebrates, transcriptional co-repressors of the Groucho/transducin-like Enhancer of split (Gro/TLE) family regulate a number of developmental mechanisms, including neuronal differentiation. The pleiotropic activity of Gro/TLE depends on context-specific interactions with a variety of DNA-binding proteins. Most of those factors engage Gro/TLE through two different types of short peptide motifs, the WRP(W/Y) tetrapeptide and the Engrailed homology 1 (Eh1) sequence (FXIIXXXL). The aim of this study was to elucidate the contribution of WRP(W/Y) and Eh1 motifs to mammalian Gro/TLE anti-neurogenic activity. Here we describe point mutations within the C-terminal WD40 repeat domain of Gro/TLE1 that do not perturb protein folding but disrupt the ability of Gro/TLE1 to inhibit the differentiation of cerebral cortex neural progenitor cells into neurons. One of those mutations, L743F, selectively blocks binding to Hes1, an anti-neurogenic basic helix-loop-helix protein that harbors a WRPW motif. In contrast, the L743F mutation does not disrupt binding to Engrailed1 and FoxG1, which both contain Eh1 motifs, nor to Tcf3, which binds to the Gro/TLE N terminus. These results demonstrate that the recruitment of transcription factors harboring WRP(W/Y) tetrapeptides is essential to the anti-neurogenic function of Gro/TLE1.

Transcriptional co-repressors of the Groucho/transducin-like Enhancer of split (Gro/TLE) family play critical roles during multiple developmental processes, including neuronal differentiation in the developing mammalian forebrain (1). Gro/TLEs act as co-repressors for a variety of DNA-binding transcription factors. Some of those proteins are dedicated transcriptional repressors while others mediate repression or transactivation depending on specific contexts (1–4). Through interactions with a large number of transcriptional regulators, Gro/TLEs are involved in the gene regulatory functions of a variety of signaling pathways, including Notch, Wnt/Wingless, transforming growth factor-β superfamily, and epidermal growth factor receptor signal transduction mechanisms (1–6). Moreover, growing evidence suggests important roles for Gro/TLEs in integrating these different signaling cascades during several developmental processes (1, 5).

The regulation of neuronal differentiation was one of the first functions of Gro/TLE proteins to be characterized. During Drosophila neural development, Gro participates in the Notch-mediated lateral inhibition mechanism that restricts the number of committed neuroblasts within proneural clusters containing initially equipotential presumptive neural progenitor cells (7, 8). Neuroblasts undergoing commitment activate the Notch receptor in adjacent cells, resulting in the transcriptional induction of genes encoding basic helix loop helix (bHLH) proteins of the Hairy/Enhancer of split (Hes) family. These DNA-binding proteins recruit Gro to form complexes that repress the expression, as well as biochemical activity, of proteins that promote neuronal differentiation, like the bHLH factors encoded by achaete-scute complex and atonal genes (9–11). Loss-of-function mutations of Drosophila gro result in the differentiation of supernumerary neurons, similar to the phenotype caused by disruption of Notch or Enhancer of split genes (7, 8).

Mammalian Gro/TLE proteins also perform anti-neurogenic functions. Gro/TLE1 and Gro/TLE3 are expressed in undifferentiated neural progenitor cells of the ventricular zone of the telencephalic vesicles (12–14). Forced expression of Gro/TLE1 in the forebrain of transgenic mice causes an inhibition/delay of neuronal development in vivo (15). Similarly, exogenous expression of Gro/TLE1 in primary cultures of undifferentiated neural progenitor cells from the dorsal telencephalon causes decreased neuronal differentiation and an accumulation of proliferating progenitor cells (14).

The molecular mechanisms underlying Gro/TLE-mediated inhibition of neuronal differentiation in the mammalian forebrain remain to be defined. Gro/TLEs form complexes, and repress transcription, with a number of DNA-binding proteins expressed during forebrain neuronal differentiation. These
include, but are not limited to, bHLH proteins of the Hes family, like Hes1 (10, 14, 16, 17), forkhead box proteins, such as FoxG1 (18–20), and homeodomain proteins of the Six (21, 22), Pax (23), and Otx (24) families. Most transcription factors that bind to Gro/TLE interact with the C-terminal WD40 repeat (WD) domain of the latter and can be grouped into two main classes based on the fact that they utilize two different types of short peptide sequences to recruit Gro/TLE co-repressors. Those “repressor peptides” belong to either the WRPW(W/Y) (termed WRPW hereafter) or Engrailed homology 1 (Eh1; FIIIIXIL) motif families (1). Although different in sequence, both WRPW and Eh1 peptides bind to an overlapping, but not completely identical, site on the surface of the Gro/TLE WD domain (25).

Here we describe studies aimed at determining the contribution of different groups of transcription factors to the ability of Gro/TLE1 to inhibit the differentiation of cerebral cortex (cortical) neural progenitor cells into neurons. Our results show that Gro/TLE1 recruitment via repressor peptides of the WRPW family is essential for Gro/TLE1-mediated inhibition of neuronal differentiation. In contrast, the ability to interact with proteins that either contain repressor peptides of the Eh1 type or bind to the Gro/TLE N terminus is not sufficient to mediate Gro/TLE1 anti-neurogenic function. These results characterize the mechanisms underlying Gro/TLE1 activity during cortical neurogenesis.

**EXPERIMENTAL PROCEDURES**

**Site-directed Mutagenesis and DNA Plasmids**—DNAs encoding mutated forms of Gro/TLE1 harboring the mutations V486S, C488R, R534A, E550K, and L743F were generated by site-directed mutagenesis using the QuikChange II mutagenesis kit (Stratagene, La Jolla, CA), and Eh1 peptides bind to an overlapping, but not completely identical, site on the surface of the Gro/TLE WD domain (25).

Here we describe studies aimed at determining the contribution of different groups of transcription factors to the ability of Gro/TLE1 to inhibit the differentiation of cerebral cortex (cortical) neural progenitor cells into neurons. Our results show that Gro/TLE1 recruitment via repressor peptides of the WRPW family is essential for Gro/TLE1-mediated inhibition of neuronal differentiation. In contrast, the ability to interact with proteins that either contain repressor peptides of the Eh1 type or bind to the Gro/TLE N terminus is not sufficient to mediate Gro/TLE1 anti-neurogenic function. These results characterize the mechanisms underlying Gro/TLE1 activity during cortical neurogenesis.

**Cortical Neural Progenitor Cell Cultures**—Primary cultures of neural progenitor cells were established from dorsal telencephalic cortices dissected from embryonic day (E) 12–14 mouse embryos as described (27–31). Cells were seeded into four-well chamber slides (Nalgene Nunc, Rochester, NY) coated with 1% poly-D-lysine and 0.2% laminin (BD Biosciences, Bedford, MA). After 48 h in vitro, cells were transfected with plasmids encoding either enhanced green fluorescent protein (GFP) alone (0.2 μg/well), or both GFP (0.2 μg/well) and Gro/TLE1 (pCMV2-FLAG-Gro/TLE1 (WT, V486S, C488R, R534A, E550K, or L743F) (1.0 μg/well). When needed, the total amount of DNA was adjusted to 1.0 μg using pcDNA3. DNA was mixed with 50 μl of OptiMEM medium (Invitrogen), followed by incubation for 5 min. An equal volume of OptiMEM medium were mixed separately with Lipofectamine 2000 reagent (Invitrogen; 2 μl/μg of DNA) and then combined with the DNA mixture and incubated for 20 min at room temperature. The DNA-Lipofectamine 2000 mixture was then added dropwise to each well. Three days later, cells were fixed and subjected to immunocytochemistry using antibodies against the proliferating cell marker Ki67 (1:200; BD Pharmingen), the neuronal progenitor cell marker nestin (1:400; Chemicon, Temecula, CA), the neuronal cell marker βIII-tubulin (1:300; Promega), the neuronal cell marker neuron specific nuclear protein (NeuN) (1:100; Chemicon), the astrocyte cell marker glial fibrillary acidic protein (GFAP; 1:300; Sigma), or activated caspase-3 (1:200; BD Pharmingen). Cells were counterstained with Hoechst 33258 (Sigma) before examination by fluorescence microscopy (14, 27, 31). Grayscale images were digitally assigned to the appropriate red or green channel using Northern Eclipse software (Empix, Ontario, Canada). Three to six random fields of each condition (per experiment) were used for quantification of the percent of GFP-positive cells co-expressing
specific markers (28–31) Results were expressed as the mean values ± S.D. At least six separate experiments were conducted in each case, and statistical analysis was performed using the Student’s t-test.

RESULTS

Characterization of Point Mutations in the WD Domain of Gro/TLE1 That Do Not Disrupt Protein Folding—Previous mutation and structural studies of WD domain containing proteins like β-transducin repeat-containing protein 1 (32), the β-subunit of G protein-coupled receptors (33, 34), and the yeast Gro/TLE analogue Tup1 (35) have revealed that residues implicated in protein-protein interactions are preferentially located at similar positions on the external surface surrounding the central channel of the β-propeller. Multiple blades and residues are implicated in those interactions. More specifically, surface residues located at the start of the first β-sheet or just after the second one are often implicated in protein-protein interactions (32).

In agreement with those findings, analysis of the crystal structure of the Gro/TLE1 WD domain demonstrated that one side of the central pore of the β-propeller harbors overlapping binding sites for both WRPW and Eh1 peptides (25). This common transcription factor-binding pocket contains key surface residues located within separate blades of the β-propeller. Some of those residues are essential for interaction with both WRPW and Eh1 peptides, while others are required for binding to the former but not the latter (25).

The crystal structure of the WD domain of Gro/TLE1 (25, 36) was utilized in conjunction with naturally occurring mutations at evolutionarily conserved residues in Gro/TLE-related proteins such as Drosophila Gro (25), Caenorhabditis elegans UNC-37 (37, 38), and yeast Tup1 (35, 39) to select five residues within the WD domain of Gro/TLE1 as in vitro mutagenesis targets (Fig. 1, A–C). More specifically, we generated the following mutations: V486S (similar to the Gro mutations V435A and V435L), C488R (analogous to mutations C348R in Tup1 and C437M in Gro), R534A (analogous to mutation R483H in Gro), E550K (analogous to mutations E463N in Tup1, E394K in UNC-37, and E499A in Gro), and L743F (analogous to mutation L692F in Gro) (Fig. 1D).

Based on crystallographic data (25, 36), these mutations were not expected to disrupt the overall structure of the WD domain. In agreement with this prediction, we observed that all mutated proteins migrated on denaturing polyacrylamide gels like wild-type Gro/TLE1 (Fig. 1E), were able to translocate to the nucleus (Fig. 1F), and retained the ability to repress transcription from a basally active promoter when expressed as fusion proteins with the DNA-binding domain of the yeast protein GAL4 (Fig. 2). Together, these results demonstrate that the point mutations in the WD domain of Gro/TLE1 selected for this study do not significantly perturb the structure and biochemical activity of Gro/TLE1.

Different Effects of WD Domain Mutations on the Ability of Gro/TLE1 to Interact with WRPW or Eh1 Repressor Peptides—To assess the possible effects of the WD domain mutations on the anti-neurogenic activity of Gro/TLE1, we first determined whether they would block Gro/TLE1 interaction with different
transcription partners. Several Gro/TLE-binding factors that contain either WRPW or Eh1 motifs are expressed during cortical neuron development in cells where Gro/TLE1 is also expressed (18, 21–24). We therefore selected specific Gro/TLE1 transcription partners that would represent examples of different categories of proteins. The bHLH factor Hes1 was selected as a prototypical WRPW motif-bearing protein. Moreover, Hes1 is a critical regulator of cortical neurogenesis (40–42). Engrailed1 (En1) was chosen as a typical example of a protein that uses an Eh1 motif to recruit Gro/TLE proteins (43). We also examined Tcf3, as an example of a transcription partner that interacts with the N terminus, and not the WD domain, of Gro/TLE (44).

Co-transfections followed by pull-down (Fig. 3A) or co-immunoprecipitations (Fig. 3, B and C) assays showed that separate WD mutations had different effects on Gro/TLE1 ability to interact with those proteins. All mutations completely blocked or severely reduced the interaction with Hes1 (Fig. 3A), suggesting that each of those residues is important for optimal WRPW peptide recognition. In contrast, the interaction of Gro/TLE1 with En1 was disrupted only by mutations C488R, R534A, and E550K, but not by the V486S and L743F mutations (Fig. 3B). These findings show that WRPW- and Eh1 motif recognition by the WD domain of Gro/TLE1 is mediated by both overlapping and separate residues. In particular, the contribution of Leu-743 is essential for WRPW peptide binding but not for Eh1 motif recognition. In contrast to the results with Hes1 and En1, all Gro/TLE1 WD mutations retained the ability to bind to Tcf3 (Fig. 3C). In agreement with this finding, each mutated protein repressed trans-activation mediated by β-catenin/Tcf complexes in transfected cells (data not shown). These results are consistent with the notion that Tcf/Lef proteins interact with the N-terminal domain of Gro/TLE (44).

We next examined the ability of mutated Gro/TLE1 proteins to bind to the forkhead transcription factor FoxG1, which is a critical regulator of telencephalic neurogenesis (45). Previous in vitro studies have suggested that Gro/TLE1 binds to FoxG1...
Regulation of Gro/TLE1 Anti-neurogenic Activity

**A**

**FLAG-Gro/TLE1:**

- **FLAG-FoxG1:**

  - INPUT (WB anti-FLAG)
  - IP anti-Gro/TLE1 (WB anti-FLAG)

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  - Gro/TLE1
  - FoxG1

**B**

**FLAG-Gro/TLE1:**

- **FLAG-FoxG1:**

  - WB anti-FLAG
  - IP anti-Gro/TLE1 (WB anti-FLAG)

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  - Gro/TLE1
  - FoxG1

**FIGURE 4. Effect of different Gro/TLE1 WD domain mutations on interaction with FoxG1.** A, HEK293 cells were co-transfected with plasmids encoding FLAG epitope-tagged WT or mutated Gro/TLE1 proteins, as indicated, and FLAG-tagged FoxG1. Each cell lysate (INPUT) was subjected to immunoprecipitation (IP) with an anti-Gro/TLE1 antibody. Immunoprecipitates, together with 1:10 of each input lysate, were subjected to SDS-polyacrylamide gel electrophoresis on either 6% (lanes 1–8) or 10% (lanes 9–14) gels, followed by Western blotting (WB) with an anti-FLAG antibody. B, HEK293 cells were co-transfected with the indicated combinations of proteins, followed by fractionation of cell lysates on a 6% SDS-polyacrylamide gel and Western blotting with an anti-FLAG antibody. Asterisks are placed next to the slower form of Gro/TLE1 observed in selected cases in the presence of FoxG1.

Analysis of Gro/TLE1 proteins on low percentage polyacrylamide gels allowed the resolution of separate Gro/TLE1 species with different electrophoretic mobility (Fig. 4A, lanes 1–7, and Fig. 4B). Reduced electrophoretic mobility of Gro/TLE1 has been shown previously to result from increased phosphorylation, a process that is promoted by interaction with several transcription partners, including FoxG1, and is referred to as “cofactor-activated phosphorylation” (14, 16). We found that mutations that reduced binding to FoxG1, such as V486S, C888R, and R534A, also reduced the increased phosphorylation of Gro/TLE1 observed in the presence of FoxG1 (Fig. 4B, see lanes 2–5). Importantly, mutation E550K, which does not prevent binding to FoxG1, completely blocked the cofactor-activated phosphorylation of Gro/TLE1 (Fig. 4B, lane 6). These findings suggest an essential role for Glu-550 in the regulation of Gro/TLE1 phosphorylation, possibly by mediating protein-protein interactions with critical factors.

Taken together, these results suggest that different WD domain mutations provide a useful means of uncoupling transcription repression partner recognition, permitting the examination of the specific contributions of separate protein classes to the biological functions of Gro/TLE1.

**Requirement for WRPW Motif Recruitment for Gro/TLE1 Anti-neurogenic Activity—**Forced expression of Gro/TLE1 inhibits/delays cortical neural differentiation in the telencephalon of developing transgenic mouse embryos and cultures of cortical neural progenitor cells (14, 15). To clarify the contribution of transcription factors containing WRPW or Eh1 motifs to its anti-neurogenic function, we exogenously expressed wild-type or mutated Gro/TLE1 proteins in primary cultures of neural progenitor cells obtained from dissected dorsal telencephalon from E12-E14 mouse embryos (Fig. 5, A and B). This defined primary culture system (“cortical progenitor cells”) has been used on multiple occasions to investigate the functions of extrinsic and intrinsic regulators of cortical neuron differentiation (27–31, 46–49). Enhanced GFP was co-expressed with Gro/TLE1 to visualize the transfected cells, which were analyzed for the expression of markers of proliferating cells, undifferentiated neural progenitors, postmitotic neurons, or astrocytes after 5 days in vitro (Fig. 5B and data not shown). As previously described (14), exogenous expression of wild-type Gro/TLE1 resulted in an increase in the number of cells co-expressing GFP and the mitotic cell marker Ki67, compared with control (Fig. 5C). Wild-type Gro/TLE1 caused a similar increase in the number of nestin-positive neural progenitor cells (Fig. 5D). These effects were accompanied by a significant reduction in the number of GFP-positive cells exhibiting a neuronal morphology and expressing the neuronal cell markers, NeuN and βIII-tubulin (Fig. 5, F and G). GFAP-positive astrocytes accounted for a small fraction of the cells in culture and Gro/TLE1 expression had no detectable effect on their number (Fig. 5E). The number of transfected cells showing signs of programmed cell death, like the expression of activated caspase-3, was small under all conditions tested (Fig. 5H). These results show a role for Gro/TLE1 in delaying/inhibiting the differentiation of cortical progenitor cells into neurons.
The anti-neurogenic effect of Gro/TLE1 was abolished by mutations that selectively disrupt interaction with WRPW, but not Eh1, repressor peptides, such as V486S and L743F (Fig. 5, C and D, F and G). The E550K mutation, which prevents interaction with Hes1 and En1 but does not block binding to FoxG1, also abrogated the anti-neurogenic affect of Gro/TLE1 (Fig. 5, C and F). The same was true for mutations, like C488R and R534A, which disrupt the interaction of Gro/TLE1 with Hes1 and Foxg1, but not Tcf3 (Fig. 5, C and D, F and G). None of the mutated Gro/TLE1 proteins caused significant changes in the number of cells expressing GFAP or activated caspase-3 (Fig. 5, E and H). Taken together, these results indicate that the anti-neurogenic activity of Gro/TLE1 depends on the recruitment of WRPW motif family proteins. They suggest further that Hes family members are the primary anti-neurogenic partners of Gro/TLE1 during cortical neuron development.

DISCUSSION

In this report, we sought to determine whether the ability of Gro/TLE1 to inhibit/delay the transition of cortical progenitor cells into neurons depends on interactions with proteins containing the WRPW or/and Eh1 repressor peptides, or neither of those. By analyzing a panel of WD domain mutations that selectively impair the interaction of Gro/TLE1 with different transcriptional cofactors, we have shown that WRPW motif recognition is essential for Gro/TLE1 anti-neurogenic activity.

Essential Role of Specific WD Domain Residues in Repressor Peptide Recognition—Using information derived from previous structural and genetic studies, we generated a panel of point mutations within the C-terminal WD domain of Gro/TLE1 that do not disrupt the overall structure of this β-propeller, as indicated by the ability of the mutated proteins to translocate to the nucleus and repress
both basal and activated transcription in transfected cells. These mutations can be grouped into two categories based on their effect on repressor peptide recognition. One group (category-1 mutations) disrupts interactions with both WRPW and Eh1 peptides whereas the second (category-2) blocks binding to the former but not the latter.

Mutations C488R, R534A, and E550K behaved as category-1 mutations in our study. Those three residues sit near the mouth of the central pore of the β-propeller (25, 36) and participate in key interactions with the C-terminal tryptophan, N-terminal tryptophan, and arginine of the WRPW peptide, respectively (25). In the case of the Eh1 motif (FXIXXIL), those residues make key contacts with leucine 7, phenylalanine 1, and isoleucine 3, respectively (25). The essential roles of those amino acids are further highlighted by their evolutionary conservation among Gro/TLE orthologs and analogs and the severe effects of naturally occurring mutations at those sites. More specifically, amino acid positions corresponding to Glu-550 in Gro/TLE1 are conserved in Drosophila Gro (Glu-499), C. elegans UNC-37 (Glu-394), and yeast Tup1 (Glu-463). Mutations targeting this position were found for Tup1 (E463N) (39) and UNC-37 (E394K) (38). In both cases, these mutations significantly perturb the biological functions of these proteins. Similarly, the position equivalent to Arg-534 of Gro/TLE1 is mutated (R483H) in a Drosophila gro allele that causes widespread perturbation of the embryonic functions of this gene (25). Taken together, these observations are consistent with the notion that category-1 residues are critical for Gro/TLE protein ability to engage a large number of transcription partners.

We have found that V486S and L743F behave as category-2 mutations. Those residues are part of a hydrophobic recess located at the mouth of the central pore, and are involved in interactions with the side chain of the C-terminal tryptophan of the WRPW peptide (25). This hydrophobic depression appears to be flexible enough to accommodate the equally flexible side chains of isoleucine-3, isoleucine-6, and leucine-7 of the Eh1 motif even in the presence of Val-486 or Leu-743 mutations (this study and Ref. 25). Analysis in Drosophila shows that mutation of Leu-629 (equivalent to Leu-743 of Gro/TLE1) causes embryonic phenotypes that are somewhat weaker than those resulting from mutations of WD domain residues required for interactions with both WRPW and Eh1 peptides (25), consistent with only a partial perturbation of protein-protein interactions.

The effects of the WD domain mutations on cofactor binding do not seem to be due to a generalized misfolding of Gro/TLE1, because all the mutated proteins were competent to interact with, and repress trans-activation mediated by, Tcf proteins. These observations suggest further that those mutations should not cause a generalized loss of the many functions of Gro/TLE1, as they are not predicted to affect all of its protein-protein interactions. It should be noted, however, that we cannot rule out the possibility that at least some of those mutations might disrupt interactions with global cofactors that bind to the WD domain and are required by most, if not all, transcription partners, including those that bind to the N terminus of Gro/TLE1.

Uncoupling of Repressor Peptide Recognition Reveals an Essential Role for WRPW Motif Recognition in Gro/TLE1 Anti-neurogenic Activity—The present studies show that category-1 mutations, which block Gro/TLE1 ability to interact with both WRPW and Eh1 peptides, also disrupt its inhibitory effect on cortical neuron differentiation. Category-2 mutations, which do not prevent binding to proteins that harbor an Eh1 motif (like En1 or FoxG1) or proteins that bind exclusively to the Gro/TLE1 N-terminal Q domain (like Tcf3), also disrupt Gro/TLE1 anti-neurogenic function. These results indicate that the ability to become recruited by transcription factors that either belong to the Eh1 peptide group or engage Gro/TLE via the N-terminal region of the latter is not sufficient to mediate Gro/TLE1 anti-neurogenic activity. Thus, even though members of these protein groups are expressed in forebrain progenitor cells, they do not appear to be involved in Gro/TLE1-mediated inhibition of cortical neurogenesis. Instead, our findings show that Gro/TLE1 depends on interactions with proteins containing WRPW motifs to inhibit the cortical progenitor-to-neuron transition.

This interpretation agrees with several previous findings. Hes1 (a prototypical WRPW motif protein) and Gro/TLE are co-expressed in cortical neural progenitor cells, form complexes, and repress transcription together (14, 16, 18, 20). Moreover, both Hes1 and Gro/TLE1 were shown to associate in cultured neural stem cells with the promoter of pro-neuronal genes, like Mash1 (17). Misexpression of Gro/TLE1 in the developing forebrain causes reduced neuronal differentiation in vivo, as does its exogenous expression in cultured cortical neural progenitor cells (Refs. 14, 15 and this study). These effects are similar to the inhibition of neuronal differentiation and maintenance of neural stem/progenitor cells caused by misexpression of Hes1, Hes3, or Hes5 in the embryonic brain (41, 50, 51). Conversely, Hes1:Hes5 double knock-out mice show a premature differentiation of neural stem/progenitor cells into neurons (52). Together with our present findings, these results strongly suggest that Gro/TLE1 works together with Hes proteins to regulate the transition of cortical neural progenitor cells into neurons.

The physiological significance of the ability of Gro/TLE1 to form complexes with other factors expressed during cortical neurogenesis remains to be defined. It is possible that through such interactions Gro/TLE1 might participate in mechanisms important for other cellular processes, like the regulation of the rate of cell proliferation of neural progenitors, or the specification of selected neuronal fates. In that regard, previous studies have shown that different Gro/TLE family members continue to be expressed in different populations of post-mitotic cortical neurons, suggesting non-overlapping roles in the establishment and/or maintenance of neuronal identity (47, 53).

Gro/TLE family members regulate a large number of developmental processes. The availability of mutations that selectively perturb interactions with specific families of Gro/TLE transcription partners is expected to facilitate the elucidation of the molecular mechanisms underlying the pleiotropic activities of this family of transcriptional co-repressors.

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Regulation of Gro/TLE1 Anti-neurogenic Activity

REFERENCES