Multiple Regions of ETO Cooperate in Transcriptional Repression*

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Daniela Hildebrand, Jens Tiefenbach, Thorsten Heinzel, Manuel Grez, and Alexander B. Maurer‡

From the Georg-Speyer-Haus, Institute for Biomedical Research, Paul-Ehrlich Strasse 42-44, 60596 Frankfurt, Germany

In acute myeloid leukemias (AMLs) with t(8;21), the transcription factor AML1 is juxtaposed to the zinc finger nuclear protein ETO (Eight-Twenty-One), resulting in transcriptional repression of AML1 target genes. ETO has been shown to interact with corepressors, such as N-CoR and mSin3A to form complexes containing histone deacetylases. To define regions of ETO required for maximal repressor activity, we analyzed amino-terminal deletions in a transcriptional repression assay. We found that ETO mutants lacking the first 236 amino acids were not affected in their repressor activity, whereas a further deletion of 85 amino acids drastically reduced repressor function and high molecular weight complex formation. This latter mutant can still homodimerize and bind to N-CoR but shows only weak binding to mSin3A. Furthermore, we could show that a “core repressor domain” comprising nervy homology region 2 and its amino- and carboxyl-terminal flanking sequences recruits mSin3A and induces transcriptional repression. These results suggest that mSin3A and N-CoR bind to ETO independently and that both binding sites cooperate to maximize ETO-mediated transcriptional repression. Thus, ETO has a modular structure, and the interaction between the individual elements is essential for the formation of a stable repressor complex and efficient transcriptional repression.

The coordinated expression of genes is required for the control of cell proliferation and differentiation during early development and homeostasis of the adult organism. Coactivator complexes containing histone acetyl transferases, such as p300/CBP and P/CAF, play a pivotal role in the regulation of gene expression and facilitate transcriptional activation by acetylating conserved lysine residues of the amino-terminal tails of core histones (1–3). Similarly, high molecular weight complexes consisting of histone deacetylases and corepressors such as N-CoR/SMRT, mSin3 and ETO1 (Eight-Twenty-One or MTG8) induce transcriptional repression when recruited by transcription factors (3–8). Unbalancing and perturbations of these processes are the causes of many diseases and contribute to the development of cancer (9), as is the case for the leukemia-associated fusion genes AML1/ETO, PML/RARa, and PLZF/RARb (2, 10–12).

Apart from the association of ETO with transcriptional repression, the physiological role of the nuclear protein ETO is still largely unknown. ETO was first identified in a frequent form of acute myeloid leukemia (AML) with translocation t(8;21) (13), resulting in the AML1/ETO fusion gene, which occurs in about 40% of cases of acute leukemia with the M2 French-American-British subtype (14, 15). In the AML1/ETO translocation product, the transactivation domain of transcription factor AML1, which would normally bind to the transcriptional coactivators p300/CBP (16), is replaced by almost the entire ETO protein. Thus, the fusion protein recruits a corepressor complex containing HDAC activity instead of the coactivators p300/CBP. The translocation partner ETO, normally expressed in brain, shows strong homology with the Drosophila nervy gene, especially in four regions named nervy homology regions (NHR 1–4). The highly conserved NHR4 region contains two zinc finger motifs and has been reported to be essential for the interaction between ETO and N-CoR/SMRT (10, 17–19). Furthermore, it has been shown that a corepressor complex containing ETO also binds to mSin3 and HDAC2 (10), although it was not clear whether these interactions are direct. Another conserved element is the amphipathic helix structure, NHR2 (20), which induces homodimerization and binding to homologous family members, such as MTG8 (21). Recent reports indicate that the oncogenic potential and transcriptional repressor activity of the translocation product AML1/ETO requires NHR2-induced dimerization and oligomerization (22). Despite the insight into the function of the oncogene AML1/ETO, the precise physiological role of ETO and its family members is yet not clear, because they show no DNA binding activity. However, they can potentiate transcriptional repression induced by other transcription factors, such as the promyelocytic leukemia zinc finger protein, by synergistically recruiting corepressors and histone deacetylase (23). In this study we define a “core repressor domain” in ETO, which contributes strongly to repressor activity, homo- and heterodimerization, and high molecular weight complex formation. Our data indicate that multiple regions of ETO work synergistically to repress transcription but have little repressor activity on their own. These data give new insights into the formation and function of the corepressor complex and may help to identify new strategies for the treatment of AML1/ETO-induced leukemias.

MATERIALS AND METHODS

Cell Culture and Plasmids—293T cells were maintained in Dulbecco’s modified Eagle’s medium (Life Technologies, Inc.) supplemented with 10% fetal calf serum (Biochrom KG, Berlin, Germany), 50 units per ml penicillin, 50 µg per ml streptomycin, and 2 mM l-glutamine (all from Life Technologies, Inc.). The expression plasmids for GAL4-ETO fusion proteins were generated by subcloning the diverse ETO DNA

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‡ To whom correspondence should be addressed. Tel.: 69-63395-223; E-mail: A.Maurer@em.uni-frankfurt.de.

The abbreviations used are: ETO, Eight-Twenty-One; AML, acute myeloid leukemia; NHR, nervy homology regions; GST, glutathione S-transferase; SDS-PAGE, SDS-polyacrylamide gel electrophoresis; ETOwt, wild type ETO; aa, amino acids; CRD, core repressor domain; HMW, high molecular weight.
fragments in frame with the GAL4 DNA binding domain (residues 1–147) of pCMX-GAL4 (5). Additional XhoI sites were introduced into pcDNA3-ETO (kindly provided by Olaf Heidenreich, Department of Molecular and Cellular Biology, University of Tubingen, Tubingen, Germany) by site-directed mutagenesis (Stratagene, La Jolla, CA) at the positions (amino acid residues 432 to 439 into pCMX-GAL4) (5). pcDNA3-ETO/XhoI-1–133 (upstream primer 5′-CGTCCCAAGCTTGTTTCTG-3′) with 0.5 mM HEPES, pH 7.8, 50 mM NaCl, 5 mM EDTA, 1 mM dithiothreitol, 0.02% Nonidet P-40 containing a protease inhibitor mixture (Roche Diagnostics GmbH), and 0.5 mM phenylmethylsulfonyl fluoride (Sigma-Aldrich) for 20 min at 37 °C. The beads were washed four times, and the bound proteins were eluted by boiling in Laemmli buffer (Roth, Germany) and subjected to SDS-polyacrylamide gel electrophoresis (PAGE). The gel was then fixed in gel drying solution (Bio-Rad) for 30 min, dried, and subjected to autoradiography.

Common precipitation Experiments—In vitro translated mSin3A was incubated with the indicated [35S]-labeled translated ETO polypeptides in 50 µl of NETN buffer (20 mM Tris, pH 8, 100 mM NaCl, 1 mM EDTA, 1 mM dithiothreitol, 0.5% Nonidet P-40) for 30 min at 37 °C. 1 µg of anti-mSin3A rabbit polyclonal antibody (R20, Santa Cruz Biotechnology, Inc., Santa Cruz, CA) or 1 µg of anti-GAL4 rabbit polyclonal antibody (Upstate Biotechnology, Lake Placid, NY) was added to the mixture, and immunoprecipitation was performed at 4 °C. 35 µl of a 50% slurry of protein A/G-agarose (Santa Cruz Biotechnology, Inc.) was then added for 1 h to precipitate the immune complexes. The precipitated proteins were then separated by SDS-PAGE, and the dried gel was subjected to autoradiography.

For coprecipitation experiments using whole cell extracts, 293T cells (5 × 10⁶ cells seeded in 10-mm-diameter dishes 24 h prior to transfection) were transfected with 20 µg of the diverse Gal4-ETO constructs. 48 h after transfection, cells were lysed in NETN buffer supplemented with 0.5 mM phenylmethylsulfonyl fluoride (Sigma-Aldrich) and a protease inhibitor mixture (Roche Diagnostics GmbH). After centrifugation for 5 min at 4 °C, the supernatants were collected and immunoprecipitated for 1 h with 1 µg of anti-mSin3A primary antibody. 40 µl of a 50% slurry of protein A/G-agarose (Santa Cruz Biotechnology, Inc.) was then added for 1 h to collect the immune complexes, which were then washed three times with NETN buffer. Further washing the blots were incubated with a peroxidase-conjugated second antibody for 30 min, and the reacted precipitated proteins were then separated by SDS-PAGE, and the dried gel was subjected to autoradiography.

Biochemical Purification of Gal4-ETO High Molecular Weight Complexes—500 µl of cell extracts obtained from 293T cells transfected with Gal4-ETO deletion mutants were loaded onto a Superose 6 HR 10/30 size exclusion column (Amersham Pharmacia Biotech) to determine the native molecular weight. The column was run in Dulbecco’s phosphate-buffered saline (PAA, Linz, Austria) supplemented with 1 mM dithiothreitol at a flow rate of 0.5 ml/min. Fractions of 1 ml were collected and analyzed for the presence of complexes containing Gal4-ETO mutants.

RESULTS

Determinants of ETO-mediated Transcriptional Repression—To functionally dissect the repressor domains of ETO and to determine their role in ETO-mediated repression, we constructed a series of amine-terminal deletion mutants leaving NHR4, the presumed binding site for the corepressor N-CoR, intact (Fig. 1A). Like other corepressors, the ETO protein cannot bind to DNA by itself. We therefore used Gal4-ETO fusion proteins to repress transcription from a reporter construct containing two Gal4 binding sites upstream of a thymidine kinase promoter driving firefly luciferase gene expression (2xUAS-thymidine kinase-luciferase) in transient assay in 293T cells. Transfection efficiencies were normalized to the activity of a cotransfected promotorless renilla luciferase reporter plasmid (pProm-Renilla Luciferase). A fusion protein of Gal4 and wild type ETO (Gal4-ETOet) showed 80-fold reduction in luciferase activity compared with a control plas-
ETO-N-CoR Interaction Requires the Presence of NHR3 and NHR4—The observation that extended amino-terminal deletions of ETO (ETOΔ1–401 and ETOΔ1–510) display drastically reduced repressor activity, prompted us to investigate whether they would be impaired in respect to binding to the corepressor N-CoR. In pull-down experiments with GST fusions of ETO mutants, a fusion protein containing NHR3 and NHR4 (GST-NHR3+4) but not NHR4 alone (GST-NHR4) interacted with N-CoR (Fig. 2). Together with the repressor activity (Fig. 1), these data suggest that N-CoR binding per se is not sufficient to mediate significant transcriptional repression. We mapped the minimal ETO binding site of N-CoR between aa 1147 and 1213, because a Gal4-N-CoR construct containing aa 970–1258 (Fig. 2), but not a smaller fragment (Gal4-N-CoR 970–1147) or a more carboxyl-terminal region (Gal4-N-CoR 1213–1502), can be precipitated by GST-NHR3+4 (data not shown).

A “Core Repressor Region” Confers Transcriptional Repression by ETO—Because NHR3 and NHR4 do not have substantial repressor activity on their own, despite binding to N-CoR, we investigated which other regions in ETO contribute to repressor activity. To this end we generated internal and carboxyl-terminal deletions of a Gal4-ETO deletion mutant (Gal4-Δ1–236) that showed maximum repression in our assay system. Removing the region between NHR2 and NHR3 (Gal4-Δ1–236ΔC; Δaa 384–432) reduced repressor activity to 49.3% repression compared with 102.6% repression with Gal4-Δ1–236 (Fig. 3B). To evaluate the role of NHR2, we deleted the NHR2 region to generate the construct Gal4-Δ1–236ΔNHR2. This deletion reduced transcriptional repression to 24.3% of Gal4-ETOwt levels (Fig. 3B). To our surprise, a construct containing 196 amino acids, including the central NHR2 domain and surrounding regions (Gal4-CRD; aa 236–432) but lacking the N-CoR binding site, showed significant repressor activity (42.7% of Gal4-ETOwt; Fig. 3B). This region of ETO was designated “core repressor domain” (CRD). Gal4-ETO fusions containing only subfragments of the core repressor domain were considerably less effective in repressing transcription. A fusion of Gal4 with a region between NHR1 and NHR3 (Gal4-N; aa 236–306) conferred only 1.7% repression, whereas a region between NHR2 and NHR3 (Gal4-C; aa 384–432) or the NHR2 region alone (Gal4-NHR2; aa 321–388) induced 8.8 and 13.5% repression, respectively (Fig. 3B). From these data we conclude that ETO requires all but its first 236 amino acids to induce maximal repression, whereby a region containing NHR2 and neighboring amino-terminal and carboxyl-terminal sequences (CRD)
represents the smallest deletion construct conferring significant repressor activity on its own.

mSin3A Interacts Strongly with the Core Repressor Domain—Based on these results we tested whether the core repressor domain binds to another corepressor molecule, mSin3A. We performed immunoprecipitation experiments using in vitro translated mSin3A together with in vitro translated 35S-labeled mutants of ETO. An antibody against mSin3A co-precipitated full-length ETO, amino-terminally deleted ETO (Gal4-CRD), and carboxyl-terminally deleted ETO (Gal4-C), indicating that the interaction domain is placed within the core repressor domain (Fig. 4). To further map the ETO-mSin3A interaction, we tested internal deletion mutants of ETO. Interestingly, constructs where NHR2 (Gal4-D1–236), the carboxyl-terminal region between NHR2 and NHR3 (Gal4-D1–236C), or the amino-terminal 85 amino acids (Gal4-D1–321) are deleted showed reduced or no binding to mSin3A (Fig. 4). As expected, no mSin3A interaction was seen with a construct containing only the carboxyl-terminal NHR3 and NHR4 regions (Gal4-D1–401). Furthermore, we could not detect coprecipitation of mSin3A with ETO deletions that contained only the amino-terminal (Gal4-N) or the carboxyl-terminal sequences (Gal4-C; data not shown) surrounding NHR2 or NHR2 (Gal4-NHR2) alone. However, ETO mutants containing NHR2 and the carboxyl-terminal region (Gal4-NHR2+C; aa 321–432) or NHR2 and the amino-terminal region (Gal4-N+NHR2; aa 236–389) were still able to interact weakly with mSin3A (Fig. 4).

These results were confirmed using cellular extracts from 293T cells transfected with Gal4-ETO deletion constructs. All ETO mutants containing the core repressor domain could be coimmunoprecipitated with an antibody against Sin3A (Fig. 5). We found strong interaction of Sin3A with Gal4-ETOwt, Gal4-D1–236, and the construct containing only the core repressor domain (Gal4-CRD) by coprecipitating 10 to 20% of ETO protein in cellular lysates with an antibody to Sin3A. In contrast, 10-fold less ETO protein (1–2% of input) could be coprecipitated with Sin3A from cellular lysates that expressed ETO mutants lacking the amino-terminal region of the core repressor domain (Gal4-D1–321) or the NHR2 region (Gal4-D1–401). No interaction could be found with shorter mutants consisting only of NHR2 and the neighboring carboxyl-terminal region (Gal4-NHR2+C) or a Gal4 fusion with NHR3 and NHR4 (Gal4-D1–401) (Fig. 5). The ETO binding site within mSin3A was mapped to the paired amphipathic helix 2 domain in mSin3A (data not shown), which has also been described to interact with the repression domain of Mad 1 (24). Interaction of N-CoR and HDAC2 with ETO was only seen with the ETOwt construct but not with the construct containing the core repressor domain (data not shown).

ETO Mutants Lacking the Carboxyl- or Amino-terminal Part of the CRD Can Still Homodimerize—Because deletion of amino- or carboxyl-terminal sequences within the CRD led to impaired repressor activity, we investigated whether these mutants are defective in NHR2-mediated homodimerization. NHR2 has been shown to induce homo- and heterodimerization between ETO and related family members such as MTGR1 (21). All constructs containing the NHR2 domain, but not those lacking NHR2 (e.g. Gal4-D1–236ΔNHR2), were able to bind to GST-ETO in pull-down experiments, confirming the structural integrity of NHR2 (Fig. 6). Homodimerization was also seen in a construct, Gal4-D1–321, that showed only little repressor activity (22.5%, Fig. 1B), indicating that ETO repressor activity depends only in part on the NHR2 amphipathic helix structure, whereas a proline-rich region amino-terminal to NHR2 appears to be critically required for maximum repressor activity.

Integrity of ETO Protein Is Required for Stable High Molecular Weight Complex Formation—In a recent paper by Minucci et al. (22), high molecular weight (HMW) complex formation was shown to be required for efficient repressor activity of AML-ETO, PML-RAR, and promyelocytic leukemia zinc finger-RAR. To investigate the ability of our constructs to form HMW complexes, we expressed various Gal4-ETO mutants in 293T cells and determined the molecular weight of the complexes by size-exclusion chromatography. HMW complexes obtained with Gal4 fusions of full-length ETO had an apparent molecular mass of 1,600 kDa. Similarly, ETO deletions Δ1–236, Gal4-D1–236ΔNHR2, and Δ1–321 formed complexes with the same mo-
The leukemia-associated protein ETO is based on a modular structure that mediates high molecular weight complex formation and maximum transcriptional repression. Furthermore, we have defined a core repressor domain containing NHR2 and the neighboring carboxyl- and amino-terminal sequences that mediates strong interaction with Sin3A and represents the smallest deletion with significant, albeit reduced repressor activity. NHR1 (25), however, which shows sequence similarity to a central 80-amino acid region of the transcriptional coactivators hTAF 130 (TBP-associated factor 130), hTAF 105, and Drosophila TAF 110 (21, 26–28), is not required for repressor function in the context of our experimental system. This is in agreement with published data showing that deletion of NHR1 does not affect ETO-mediated repression of the MDR-1 promoter. In this context it is worth noting that although a lack of NHR1 did not effect repressor activity, it destabilized the formation of high molecular weight complexes, as indicated by the appearance of smaller-sized complexes compared with ETOwt.

The fourth homology region (NHR4) consists of two zinc finger domains that are necessary for ETO-N-CoR/SMRT interaction. Deletion, or even point mutations, of this region completely abolish binding of ETO to N-CoR/SMRT but reduce transcriptional repression only partially (10, 18, 19). This is in agreement with our data showing that the core repressor domain alone mediates 50% of ETOwt repressor activity, although it recruits only Sin3A but not N-CoR. Furthermore, we present evidence that the NHR4 zinc finger motif alone is not capable of interacting with the ETO binding region in N-CoR, which we mapped within N-CoR repressor domain III. ETO-N-CoR interaction requires both the presence of the zinc finger motif and the adjacent helical structure of NHR3. In experiments similar to ours, Zhang et al. (29) could also demonstrate binding of the highly homologous corepressor SMRT to an ETO mutant containing NHR3 and NHR4 fused to the Gal4 DNA binding domain. We conclude that NHR4 is necessary but not sufficient to recruit N-CoR. Interestingly, the binding site for N-CoR (NHR3 and NHR4) did not induce transcriptional repression, suggesting that the interaction may be unable to efficiently recruit histone deacetylases. However, N-CoR binding may serve to enhance repression by stabilizing the corepressor complex with other corepressors that are needed to induce repressor activity.
Recent evidence indicates that the oncogene AML1/ETO requires homodimerization, mediated by the amphipathic helix structure NHR2 (17, 21), to form HMW complexes and induce transcriptional repression (22). We were able to confirm that the stability and size of these complexes correlate with repressor function, entrusting an important role to the core repressor domain for the correct formation of HMW complexes. This was demonstrated with ETO constructs lacking structural elements of the CRD, such as NHR2, the amino-terminal 85 amino acids, or the carboxy-terminal region, which not only had reduced repressor activity but also led to the formation of complexes with a lower molecular weight. Interestingly, both Gal4-ETO mutants lacking either the amino-terminal or the carboxy-terminal region of the core repressor domain (Gal4-Δ1–321 and Gal4-Δ1–236ΔC) were still perfectly able to dimerize with full-length ETO, indicating that the amphipathic helix structure of NHR2 was functional. These ETO deletions were, however, severely impaired in binding to Sin3A. We conclude that repressor activity and HMW complex formation are not solely determined by the process of NHR2-induced dimerization but also through the affinity of the ETO molecule to Sin3A. In this context it is worth noting that only ETOwt or the deletion construct Gal4-Δ1–236 could be eluted in the same fraction as complexes containing Sin3A (data not shown). The ETO-Sin3A interaction, however, appears to be more complex than anticipated. We were still able to detect weak binding of Sin3A to ETO mutants lacking NHR2 and sequences amino-terminal of NHR2 in cellular lysates. Similar results have also been obtained in Cos-7 cells overexpressing mSin3A and ETO deletion mutants (10), showing that binding of mSin3A to ETO under these conditions occurs even in the absence of NHR2 (10). This may indicate that Sin3A interacts with ETO not only directly, but also indirectly through other corepressor molecules (5, 30, 31). To reduce the possibility of indirect interactions via secondary molecules, we tested ETO-Sin3A interaction with in vitro translated proteins. These experiments, however, support our in vitro data showing weak interaction of mSin3A with ETO constructs lacking sequences of the core repressor domain. Our data favor a model in which complex structural requirements are needed for stable direct interaction of Sin3A with ETO, whereas the indirect interaction of Sin3A to ETO through binding to N-CoR and HDAC2 is not sufficient to induce repressor activity.

Because Gal4-ETO mutants with deletions in the mSin3A binding site/core repressor domain were impaired in their ability to repress transcription, and neither the Sin3A binding site (CRD) nor the N-CoR binding site (NHR3 and NHR4) were able to induce maximum transcriptional repression or HMW complex formation by themselves, we conclude that these two major domains in ETO cooperate for optimal function. Although these results have been obtained in transient transfection assays and may not properly reflect the physiological situation at endogenous chromosomal loci (32), it raises the question why binding to one corepressor molecule is not sufficient for ETO to induce optimal repression. It appears that the corepressor complex requires a certain stability, possibly mediated by the interaction of corepressor molecules with each other. The concept that complexes with multiple interacting subunits are required in the process of transcriptional regulation has also been demonstrated for coactivator complexes containing histone acetylase activity (3). The modular structure of ETO opens the possibility to interfere with one or more structural elements in the ETO molecule, thereby destabilizing complex formation and reducing repressor activity. This in turn may ultimately enable a therapeutic approach for the treatment of leukemias with the t(8;21) translocation.
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