AML1 is one of the most frequently translocated genes in human leukemia. Here we demonstrate that acute myeloid leukemia-1 (AML-1) (Runx-1) represses transcription from a native promoter, p21Waf1/Cip1. Unexpectedly, this repression did not require interactions with the Groucho co-repressor. To define the mechanism of repression, we asked whether other co-repressors could interact with AML-1. We demonstrate that AML-1 interacts with the mSin3 co-repressors. Moreover, endogenous AML-1 associated with endogenous mSin3A in mammalian cells. A deletion mutant of AML-1 that did not interact with mSin3A failed to repress transcription. The AML-1/mSin3 association suggests a mechanism of repression for the chromosomal translocation fusion proteins that disrupt AML-1.

Translocations that disrupt the AML1 gene are among the most common aberrations found in human leukemia. The t(8;21) is found in 10–15% of myeloid leukemias and gives rise to the AML-1/ETO transcriptional repressor (1–3). The t(3;21) is found in 10–15% of myeloid leukemias and gives rise to the AML-1/EAF, AML-1/MDS, or AML-1/EVI1 fusion proteins (4, 5). The t(12;21) is found in up to 30% of pediatric B-cell acute leukemia and creates the TEL/AML-1 fusion protein (6, 7). These translocation fusion proteins create transcriptional repressors that dominantly interfere with AML-1-specific transcription (5, 8, 9). AML-1 function is also abrogated by the inversion (16), which fuses the AML-1 DNA binding partner, core binding factor β (CBFβ or PEBP2β) to the smooth muscle myosin heavy chain gene MYH11, in up to 15% of acute myeloid leukemias (10, 14, 15).

AML-1 is a member of the Runt-like transcription factors (Runx-1, -2, and -3), named after the Runt protein that controls segmentation in the Drosophila embryo (11, 12). The highly conserved Run domain is the DNA binding motif in this family of proteins. AML-1 appears to act as an “organizing” factor for many promoters and enhancers by interacting with co-activators and other DNA binding transcription factors (18–27).

Both Runt and a second Drosophila runt-like protein Lox- enge can repress as well as activate transcription (17, 28). In addition, when fused to the DNA binding domain of GAL-4, Runx family proteins repressed transcription through GAL4 DNA-binding sites (28). AML-1 interacted with the Groucho co-repressor in yeast two-hybrid assays, and the Groucho binding domain contributed to repression, but it was not sufficient for full activity (28). As well, AML-1 cooperated with LEF-1 to repress transcription of the T-cell receptor ζ enhancer, and this repression was partially dependent on the Groucho binding domain (29). Thus, AML-1 may act as a master regulator that facilitates the assembly of protein complexes for transcriptional activation or transcriptional repression in a cell type-specific manner.

We have established an assay for AML-1β-dependent repression using the cyclin-dependent kinase inhibitor p21Waf1/Cip1 promoter (AML-1B is the largest isoform of AML-1(9)). Repression was not mediated by the Groucho binding motif. This led us to identify an association between AML-1B and the mSin3 co-repressors. An AML-1B protein containing a deletion of the mSin3A binding domain lacked the ability to repress transcription. These results define a mechanism for AML-1-dependent repression.

**EXPERIMENTAL PROCEDURES**

**Cell Culture and Plasmids—**C33A cells and Cos-7 cells were maintained in Dulbecco’s modified Eagle’s medium (BioWhittaker Inc, Walkersville, MD) containing 10% fetal bovine serum, 50 units/ml penicillin, 50 μg/ml streptomycin, and 2 mM l-glutamine (BioWhittaker). NIH 3T3 cells were maintained in Dulbecco’s modified Eagle’s medium containing 10% bovine serum. HEL cells were cultured in RPMI 1640 (Bio-Whittaker) containing 10% fetal bovine serum, antibiotics, and l-glutamine. pCMV5-AML1B and deletion plasmids have been previously described (30). AML-1B-(del 208–237) and AML-1B-(del 275–314) were created by polymerase chain reaction with the insertion of a BglII restriction site to join the fragments. Each fragment was fully sequenced to confirm that no other mutations were introduced by polymerase chain reaction. The GAL4 fusion cDNAs were prepared by subcloning the indicated fragments, in frame, with the GAL4 DNA binding domain (residues 1–147) using the pCMV series vectors (31).

**Co-Immunoprecipitations and Immunoblotting—**Cos-7 cells (3 × 10⁶ cells in 100-mm dishes) were transfected using LipofectAMINE (Life Technologies, Inc.) with 3.5 μg of expression plasmids. For metabolic labeling, Cos-7 and HEL (1 × 10⁶) cells were incubated for 3 h with 100 μCi of [35S]methionine. Cells were extracted with phosphate-buffered saline supplemented with 1 mM EDTA, 1.5 mM MgCl₂, 0.2 mM phenylmethylsulfonfyl fluoride, and 0.1 trypsin inhibitory unit/ml

A mechanism of repression by acute myeloid leukemia-1, the Target of Multiple Chromosomal Translocations in Acute Leukemia*

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AML-1B Binds mSin3 to Repress Transcription

Fig. 1. AML-1 represses transcription from the p21Waf1/Cip1 promoter. A, schematic diagram of the promoters tested and AML-1B-mediated repression. B, the Groucho binding motif does not contribute to AML-1B-mediated repression. NIH 3T3 cells were transfected with 1.0 μg of the indicated human p21Waf1/Cip1 (WWP-luciferase)-firefly luciferase plasmids, 500 ng of the cytomegalovirus immediate early promoter-secreted alkaline phosphatase plasmid (pCMV-SEAP) as an internal control, and 2 μg of the indicated pCMV5-AML-1B plasmids. A schematic diagram of the AML-1B deletions is shown in Fig. 3A.

A

| Promoter | Fold Rep |
|----------|----------|
| WWP-luciferase | 4.5±0.5 |
| 2 sites | 1.3±0.2 |
| 1 site | 1.8±0.1 |
| Del Pat | 1.5±0.2 |

B

- **AML-1 Represses the p21Waf1/Cip1 Promoter**—When the C terminus of Runt or AML-1 family proteins was fused to the GAL4 DNA binding domain, these fusion proteins repressed transcription 3–4-fold (28). To establish an AML-1-dependent repression assay, we tested native promoters containing AML-1-binding sites in various cell types. The p21Waf1/Cip1 repression assay, we tested native promoters containing AML-1-binding sites, we found that AML-1B repressed transcription from the p21Waf1/Cip1 promoter by 5–10-fold (Figs. 1 and 5). Deletion analysis indicated that sequences 5′ to the second AML-1-binding site were required for promoter-specific repression (Fig. 1A).

Next, we asked whether the Groucho co-repressor contributed to this repression. Unexpectedly, removal of the Groucho interaction site (residues 476–480) by deletion of the last 11 amino acids (aa) or the C-terminal 99 aa (residues 382–480) did not significantly impair AML-1-mediated repression (1–469 and 1–381, respectively, Fig. 1B).

**AML-1 Associates with the mSin3 Co-repressors**—To determine the mechanism of AML-1B-dependent repression, we tested whether AML-1B interacts with known co-repressors in mammalian cells. Cell lysates from Cos-7 cells transiently expressing AML-1B were immunoprecipitated with two different AML-1 antibodies (α-RHD and α-AML-1-N), and the presence of co-repressors in the immune complexes was determined by immunoblot analysis. Both AML-1 antibodies co-immunoprecipitated the mSin3A co-repressor only when AML-1B was expressed (Fig. 2A, left panel, last 2 lanes).

To confirm this result, we performed the reciprocal experiment. Because AML-1B co-migrates with the heavy chain, we could not use immunoblotting. Therefore, cells transiently expressing AML-1B were metabolically labeled, and cell lysates were immunoprecipitated with anti-mSin3A in the presence of 0.5% Triton X-100, 0.5% deoxycholic acid, and 0.5% SDS. AML-1B efficiently co-immunoprecipitated with anti-mSin3A (Fig. 2B, middle lane), and the co-immunoprecipitation of AML-1B and mSin3A was blocked by the presence of the immunizing mSin3A peptide (Fig. 2B, last lane).

The amount of radiolabeled mSin3A immunoprecipitated from cells labeled for 3 h was low relative to AML-1B (Fig. 2B, middle lane). This could be due to a slow synthesis rate of the endogenous mSin3A or due to more than one AML-1B molecule associating with mSin3A. To test the former possibility, we performed the same experiment, but we labeled the cells for 30 h (Fig. 2C). Under these conditions, similar amounts of radiolabeled AML-1B and mSin3A were precipitated with anti-mSin3A IgG (Fig. 2C, lane a-Sin3A). The α-mSin3A antibody did not cross-react with AML-1B in immunoblot analysis and did not immunoprecipitate bacterially produced AML-1.2 In addition, boiling the cell lysate abrogated the AML-1B/mSin3A co-immunoprecipitation.

The interaction of AML-1B with mSin3A was stable under highly stringent conditions (0.5% Triton X-100, 0.5% deoxycholic acid, and 0.5% SDS), but these previous experiments relied on overexpressed AML-1B and endogenous mSin3A. To determine whether the endogenous proteins associate, we immunoprecipitated mSin3A from metabolically labeled HEL cells. The mSin3A antibody recovered a number of associated proteins (Fig. 2D, first lane). Two of these proteins co-migrated with AML-1 proteins immunoprecipitated with anti-AML-1 (Fig. 2D, 1st lane, note that AML-1 migrated as a doublet). AML-1 could be re-immunoprecipitated from the mSin3A immune complexes (Fig. 2D, last lane) but not when the immunizing peptide was added to the lysate prior to antibody addition (Fig. 2D, next to last lane).

The mSin3 protein family includes mSin3A and the homologous mSin3B protein. By having established an interaction with mSin3A, we asked whether AML-1B could also interact with mSin3B. After transient expression of AML-1B and metabolic labeling, AML-1B was co-immunoprecipitated with endogenous mSin3B using a C-terminal (Fig. 2E, last lane) but not an N-terminal antibody (Fig. 2E, middle lane). It is possible that by interacting with mSin3B, AML-1B obscures the anti-N-terminal antibody epitope.

AML-1 is a member of a gene family that includes two highly

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Fig. 2. AML-1B interacts with mSin3A. A, mSin3A (Sin) co-immunoprecipitates with AML-1B. Cos-7 cells were transfected with pCMV5-AML-1B. Cell extracts (6 mg of total protein) were immunoprecipitated (IP) with anti-N-terminus (α-AML-1-N) or anti-RHD AML-1 (α-RHD) IgG, and mSin3A was detected by immunoblot. Mock and AML-1 refer to non-transfected pCMV5-AML-1B-transfected, respectively, B, AML-1B co-immunoprecipitates with mSin3A. Cells were transfected with pCMV5-AML-1B, metabolically labeled as described under “Experimental Procedures,” and cell extracts (1 mg) immunoprecipitated with mSin3A antibodies in the absence or presence of 10 μg of antigenic peptide (pep). C, AML-1B/mSin3A co-immunoprecipitation after an extended labeling period. Cos-7 cells were transfected with pCMV5-AML-1B, labeled for 30 h, and immunoprecipitated as in B. D, endogenous AML-1B and mSin3A associate. HEL cells were metabolically labeled and lysed in phosphate-buffered saline containing 0.5% Triton X-100 and protease inhibitors, followed by immunoprecipitation with mSin3A antibody (lanes 1–237) or anti-mSin3A IgG (lanes S), mSin3A was detected by immuno blot. Mock and AML-1 refer to non-transfected pCMV5-AML-1B-transfected, respectively. E, AML-1B co-immunoprecipitates with mSin3A. AML-2 or pCMV5-PEBP2B-transfected, respectively.

The AML-1 SID Is Required for AML-1-dependent Repres-

Definition of the AML-1 mSin3A Interaction Domain—To identify the AML-1B mSin3A interaction domain (SID), wild-type AML-1B and AML-1B mutants containing internal deletions (Fig. 3A) were expressed, and metabolically labeled cell lysates were immunoprecipitated with anti-AML-1 (Fig. 3B, lanes A) or anti-mSin3A (lanes S). Deletions encompassing residues 275–480 did not impair mSin3A binding, but deletion of residues 208–237 eliminated the interaction between AML-1B and mSin3A (Fig. 3B, 4th lane from left).

To determine whether this region of AML-1 was sufficient for mSin3A binding, we used a series of GAL4-AML1B fusion proteins (Fig. 3A). The GAL4 DNA binding domain contains a nuclear localization signal to ensure appropriate localization of these proteins. Cos-7 cells expressing the chimeric proteins were metabolically labeled and immunoprecipitated with anti-GAL4 (Fig. 3C, lanes G) or anti-mSin3A IgG (lanes S). AML-1B sequences C-terminal to residue 290 (Fig. 3C, lanes labeled 290–480, 351–381, or 432–480) were not sufficient for mSin3A binding (Fig. 3C). In addition, residues encompassing the last 32 aa of the runt domain (lanes labeled 172–204) failed to bind mSin3A. By contrast, the entire C terminus of AML-1B (Fig. 3C, lanes labeled 172–480) or only residues 172–290 (Fig. 3C, right panel, lanes labeled 172–290) were sufficient to mediate mSin3A association (Fig. 3C). Coupled with the deletion analysis described in Fig. 3, we conclude that a central region of AML-1 (residues 172–275) binds to mSin3A. We next localized the AML-1B interaction domain on mSin3A. The N-terminal 237 aa of AML-1B were fused to the GAL4 DNA binding domain and tested for interaction with mSin3A and C-terminal truncations of mSin3A (Fig. 4A) in the yeast two-hybrid system. These AML-1B sequences interacted with mSin3A aa 76–693 when fused to the GAL4 transcriptional activation domain as measured by growth on adenine-deficient media (Fig. 4, B and C). Deletion of mSin3A residues 480–693 eliminated the AML-1B/mSin3A interaction (Fig. 4, B and C), indicating that these sequences, including the third amphipathic helix (PAH 3), are needed for AML-1 interactions (Fig. 4, B and C). In addition, the interaction of AML-1 aa 1–237 with mSin3A further localizes the AML-1B SID to residues 172–237.

The AML-1 SID Is Required for AML-1-dependent Repres-
To determine whether the AML-1B SID is required for repression, we tested the panel of AML-1B deletion mutants (Fig. 3A) for repression of the p21\textit{Waf1/Cip1} promoter (Fig. 5A). Deletion of residues 208–237, which eliminates the interaction between mSin3 and AML-1B \textit{in vivo}, ablated repression of the p21\textit{Waf1/Cip1} promoter. By contrast, deletion of the C-terminal WRPY motif or deletion of the C-terminal 99 aa had little or no effect on AML-1B-mediated repression (Fig. 5A). However, deletion of aa 290–387 or 290–432 also eliminated AML-1B-mediated repression (Fig. 5A). We conclude that the mSin3A interaction is necessary for repression, and a second C-terminal domain contributes to repression of the p21\textit{Waf1/Cip1} promoter by AML-1B.

mSin3 proteins repress transcription by directly interacting with the basal transcriptional machinery (38, 39) and by linking site-specific DNA-binding proteins to histone deacetylases (40). AML-1B is tightly associated with the nuclear matrix and requires ionic detergents and/or sonication to extract it from cells efficiently. Under these conditions, we were unable to demonstrate consistently an \textit{in vivo} interaction between AML-1 and histone deacetylases. Therefore, we tested the ability of a histone deacetylase inhibitor, trichostatin A, to affect AML-1B-mediated repression. Importantly, the levels of trichostatin A used in this analysis did not markedly alter expression from the p21\textit{Waf1/Cip1} promoter in NIH 3T3 cells (Fig. 5B). However, trichostatin A impaired AML-1B-dependent repression (Fig. 5B), suggesting that histone deacetylases contribute to AML-1B-mediated repression.

**DISCUSSION**

AML-1B is a transcriptional activator of numerous tissuespecific promoters and enhancers. In this report, we show that AML-1B also acts as a transcriptional repressor of the p21\textit{Waf1/Cip1} promoter. AML-1B and mSin3A interacted in yeast two-hybrid assays and by co-immunoprecipitation from mammalian cells. Although this association is observed in multiple assays, and it is maintained in the presence of ionic detergents, it is possible that this interaction is not direct but that it is mediated by an as yet unidentified protein. As well as the AML-1B SID, a second C-terminal region of AML-1B is...
required for repression (residues 290–387). This region contains putative protein interaction sites and a nuclear matrix targeting signal (41). Thus, it is likely that other co-repressors contribute to AML-1-mediated repression or that correct subnuclear localization is required.

The mSin3 co-repressors often act in cooperation with accessory proteins such as the nuclear hormone co-repressors N-CoR and SMRT and histone deacetylases (40). We determined that AML-1B (residues 1–237) and N-CoR (residues 1019–2061) interact in the yeast two-hybrid system, but we have not been able to consistently co-immunoprecipitate AML-1B and N-CoR from mammalian cells.2 Because residues 1–237 of AML-1B also interact with mSin3 proteins, this association between AML-1 and N-CoR may be indirect. Similarly, we have not been able to co-immunoprecipitate consistently histone deacetylase-1 or -2 with AML-1B.2 Again, these associations may be indirect. It is also possible that the conditions required to solubilize AML-1B (AML-1B is a component of the nuclear matrix (41)) make it difficult to preserve these weak protein interactions. Although mSin3A can also repress transcription by interacting with TFIIB (38, 39), our results with trichostatin A indicate that histone deacetylases contribute to AML-1B-mediated repression.

AML-1B can function as both a repressor and an activator of transcription. AML-1B is a weak transactivator in C33A, CV-1, and Jurkat cells but cooperates with transcription factors such as C/EBPα or Ets-1 to more strongly activate transcription (25, 42, 43). For the p21
$^{Waf1/Cip1}$ promoter, we observed a modest transactivation by AML-1B in the K562 myeloid cell line (approximately 7-fold). AML-1-dependent repression is cell type-specific as it represses p21
$^{Waf1/Cip1}$ in NIH 3T3 cells (Figs. 1 and 5). We have also observed AML-1-dependent repression of the Multidrug Resistance-1 and Rous sarcoma virus promoters in NIH 3T3 cells.3 Because mSin3 levels are similar between these cell lines,2 other factors must influence AML-1 transcriptional activity.

Whereas AML-1 can both activate and repress transcription in a cell type-specific manner, the AML-1 fusion proteins found in acute leukemia are constitutive repressors (44). The work presented here has implications for the mechanism of action of these chromosomal translocation fusion proteins. The entire SID is retained in the t(12;21), which retains nearly all of AML-1 (6, 45). We have shown that the t(12;21) can bind to mSin3 proteins, and this interaction is mediated by the AML-1 SID as well as by the pointed domain in TEL (46). Interestingly, transcriptional repression by TEL/AML-1 was abrogated by deletion of the AML-1 SID and the TEL pointed domain (8, 46, 47). Although the t(9;21) deletes most of the C terminus of AML-1 in much the same manner as the t(8;21), the t(3;21) breakpoint can retain the entire AML-1 SID (5). We are currently investigating a role for mSin3 in AML/EVI1 transcriptional repression. Coupled with the utilization of the mSin3 co-repressors by the t(8;21), the t(15;17), and t(11;17) in acute promyelocytic leukemia (44), our work suggests that this co-repressor may be used by a significant proportion of chromosomal translocation fusion proteins. If so, mSin3A, mSin3B, and their downstream effectors (e.g. histone deacetylases) are

3 S. W. Hiebert, unpublished observations.
potential therapeutic targets in a large proportion of acute leukemias.

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