The AML-1-encoded transcription factor, AML-1B, regulates numerous hematopoietic-specific genes. Inappropriate expression of AML-1-family proteins is oncogenic in cell culture systems and in mice. To understand the oncogenic functions of AML-1, we established cell lines expressing AML-1B to examine the role of AML-1 in the cell cycle. DNA content analysis and bromodeoxyuridine pulse-chase studies indicated that entry into the S phase of the cell cycle was accelerated by up to 4 h in AML-1B-expressing 32D.3 myeloid progenitor cells as compared with control cells or cells expressing E2F-1. However, AML-1B was not able to induce continued cell cycle progression in the absence of growth factors. The DNA binding and transactivation domains of AML-1B were required for altering the cell cycle. Thus, AML-1B is the first transcription factor that affects the timing of the mammalian cell cycle.

The largest form of acute myeloid leukemia-1 (AML-1), termed AML-1B (1) (also known as Runx1, CBFA2, or PEBP2aB1(2–4)), activates the transcription of numerous tissue-specific genes, including genes encoding cytokines and cytokine receptors, T cell receptors, and myeloid-specific genes (e.g. neutrophil peptide-3 and myeloperoxidase) (5–7). When transfected alone, AML-1B activates the transcription of these genes to low levels, but it cooperatively activates transcription with cytokine receptors, T cell receptors, and myeloid-specific genes of the Cell Cycle.

Overexpression of the fusion protein encoded by the Inv (16) inhibited cell cycle progression (28). This protein can act as an AML-1 dominant repressor, suggesting a role for AML-1 in the G1 phase of the cell cycle. However, the Inv (16) fusion protein could also interact with and regulate other factors. In addition, many proteins are required for cell cycle progression, but few factors actually promote transit through the cell cycle. Therefore, we have explored the functions of AML-1 in regulating the cell cycle. We have enforced the expression of AML-1B and found that it accelerates transit through the G1 phase, whereas transcriptionally inactive forms of AML-1 do not affect the cell cycle. This phenotype is similar to that observed upon overexpression of the D- and E-type cyclins (29–31). Thus, AML-1 is one of the first transcription factors whose enforced expression shortens the G1 phase of the cell cycle.

**EXPERIMENTAL PROCEDURES**

**Cell Lines—**Parental 32D.3 myeloid progenitor cells were maintained as suspension cultures in RPMI 1640 containing 10% fetal bovine serum (BioWhittaker), 2 mM L-glutamine (BioWhittaker), 1% penicillin G-streptomycin (Life Technologies, Inc.), and 15 units/mL IL-3. 32D.3 cells stably transfected with AML-1B or derivatives thereof were constructed as described previously (32) using the sheep metallothionein promoter plasmid pMT-CB6. COS cells were cultured in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum. The designation pMT indicates a control neomycin-resistant plasmid. COX cells were cultured in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum. The designation pMT indicates a control neomycin-resistant plasmid.
For bromodeoxyuridine (BrdU) analysis, asynchronously growing cells were resuspended at 0.5 × 10^6/ml in media containing IL-3. Cells were pulse-labeled with 10 μM BrdU (Sigma) for 30 min, washed twice to remove BrdU, and resuspended in normal growth media containing IL-3. Aliquots of 2 × 10^6 cells were obtained at the indicated time points following the removal of BrdU. BrdU detection was performed by standard procedures (33). Briefly, cells were washed in cold PBS and fixed in cold 70% ethanol for 30 min. Cell pellets were then incubated for 30 min in 4 N HCl, washed in 0.1 M borax (pH 9.1) (Sigma), followed by a PBS wash. Cells were then resuspended in 50 μl of PBS-TB (PBS containing 0.5% Tween 20 (Sigma) and 0.5% bovine serum albumin Fraction V (Sigma)), and a 1:150 dilution of an anti-BrdU antibody (BU-33) (Sigma) in PBS-TB for 30 min at room temperature. After two washes in PBS-TB, cells were incubated with a 1:150 dilution of sheep fluorescein isothiocyanate-conjugated anti-mouse F(ab’2) (Sigma) in PBS-TB for 30 min at room temperature. Cells were then washed twice in PBS-TB, resuspended in PBS containing 5 μg/ml propidium iodide (Sigma), 1 μg/ml RNase A, and analyzed on a FACScalibur flow cytometer (Becton Dickinson).

**Protein Analysis**—For protein analysis, cells were lysed in microextraction buffer, sonicated, and clarified as described previously (34, 35). Total protein concentration of lysates was measured using the Bio-Rad protein assay reagent. Cell lysate (100 μg) was electrophoresed on a 10% polyacrylamide gel, transferred onto nitrocellulose, and probed with the indicated antibodies. Immune complexes were detected using the Super Signal detection system (Pierce) and a peroxidase-labeled 10% polyacrylamide gel, transferred onto nitrocellulose, and probed with the indicated antibodies. All proteins were detected using a purified rabbit polyclonal antibody specific to the runt homology domain (RHD) of AML-1. Gel mobility shift analysis and antibodies recognizing the AML family of proteins have been described (36). The anti-AML antibodies are available from Calbiochem. Gel mobility shift analysis for E2F was performed as described (35). Immunoblot analysis for cell cycle regulatory proteins was performed with antisera purchased from Calbiochem.

**Transcription Assays**—A 1.1-kilobase pair fragment of the murine cyclin D2 promoter was amplified from genomic DNA by polymerase chain reaction based on the published sequence (37). This fragment was cloned into pGL2 basic, which contains a polylinker sequence upstream of the firefly luciferase gene. The indicated promoter deletions were made using convenient endonuclease restriction sites. pGL2-D2 was co-transfected using the Superfect reagent (Qiagen) with pCMV5-AML-1B or pCMV5-AML-1B(L175D) into COS-7 cells, and luciferase activity was measured 40 h later. Secreted alkaline phosphatase activity expressed from the cytomegalovirus immediate early promoter was used as an internal control to correct for transfection efficiency. Regulation of the human thymidine kinase promoter was performed in the same manner but using the renilla luciferase as the reporter gene (Promega). The cyclin D1-luciferase promoter plasmid was a kind gift from Dr. Ronald Wisdom (Vanderbilt University School of Medicine) (38).

**RESULTS**

**Enforced Expression of AML-1B Accelerates Entry into S Phase**—The observation that the Inv (16) fusion protein inhibits cell cycle progression (28) suggested that AML-1 normally functions in the G1 phase of the cell cycle. To test this possibility, we enforced the expression of AML-1B, the largest AML-1-encoded product, to determine its effects on the cell cycle. The diploid, IL-3-dependent myeloid progenitor cell line 32D.3 was used for this cell cycle analysis because these cells express relatively low levels of AML-1B. We established 32D.3 cell lines expressing AML-1B from the zinc-inducible sheep metallothionine promoter. Single cell clones expressing AML-1B were identified from three separate parental populations by immunoblot analysis using antibodies specific for AML-1 (Fig. 1). As a control for later experiments, we also selected clonal cell lines that did not express AML-1B (labeled pMT in later figures). In addition, we isolated cell lines that expressed mutant AML-1B proteins. AML-L175D contains a single amino acid change within the DNA binding domain (also known as the runt homology domain or RHD) that disrupts DNA binding (leucine

**Fig. 1. Establishment of AML-1B-expressing 32D.3 cell lines.** Immunoblot analyses of extracts from cell lines expressing AML-1B, the DNA binding defective mutant AML-1B L175D, and AML-1a are shown. Extracts from the indicated cell lines were analyzed by immunoblot using an affinity-purified rabbit polyclonal antibody specific to the runt homology domain (RHD) of AML-1 (46). Note that for simplicity the pMT designation shown in later figures is not shown here. The number following each name indicates the single cell clone number.

175 changed to aspartic acid, labeled L175D, Fig. 1) (39), whereas AML-1a lacks the C-terminal transactivation domain (AML-1a.3, Fig. 1). Although the metallothionine promoter was used, high levels of protein expression were found in the absence of zinc. To avoid complications in the cell cycle experiments, metal induction was not used. Cell lines with higher basal expression were used for further analysis (e.g. lines 7 and 28).

To compare the rates of cell cycle progression of these cell lines, DNA content analysis was performed. Enforced expression of AML-1B appeared to affect the cell cycle, as fewer cells were present in the G1 phase and more cells accumulated in S phase in AML-1B-expressing cells versus a control cell line that was established at the same time (designated pMT, Fig. 2A). The accumulation of AML-1-expressing cells in S phase could be due to a shortening of another cell cycle phase or to a lengthening of S phase. To address this issue, we determined the timing of the cell cycle phases by performing pulse-chase analysis using the nucleotide analogue BrdU. This method avoids the use of cell cycle poisons that grossly disrupt cellular morphology and physiology. A 30-min pulse of BrdU was followed over a 24-h chase period by flow cytometry using an anti-BrdU antibody to quantitate BrdU incorporation and propidium iodide staining of DNA to measure DNA content (Fig. 2, B and C). By plotting BrdU incorporation versus DNA content we were able to observe both BrdU labeled (Fig. 2B, panel pMT3, 0 Hour area above the horizontal line, and see arrows in
FIG. 2. Cell cycle analysis of AML-1B-overexpressing 32D.3 cells. A, cell cycle analysis of AML-1B-expressing and control cell lines using propidium iodide staining and flow cytometry to measure DNA content. The pMT designates a control cell line that expresses only the neomycin resistance gene. B, BrdU pulse-chase analysis. Bivariate distributions of BrdU incorporation (y axis) versus DNA content (x axis) from the indicated cell lines following pulse-labeling (30 min) with BrdU (0 hr) and following a 10- or 12-h chase period in the absence of BrdU. Cells were washed, resuspended, and fixed as described under “Experimental Procedures” before analysis on a FACScalibur flow cytometer (Becton Dickinson) for DNA content (propidium iodide) and BrdU incorporation (fluorescein isothiocyanate). Quantitation of the numbers of BrdU-positive cells in S phase of the cell cycle was performed by applying the ModFit analysis algorithm to the indicated population of cells. The gates used for this quantitation are shown in the first panel. C, BrdU pulse-chase analysis was performed as in B but analyzed at 9 and 13 h after labeling. The arrows indicate the leading edge of the BrdU-labeled cells progressing through S phase. The arrowheads indicate the leading edge of unlabeled cells progressing through the cell cycle. The brackets in the 13-h samples indicate the trailing portion of the unlabeled cells passing through the S phase. The pMT designation indicates that the cells express AML-1B from the sheep metallothionein promoter, and the single cell clone number is indicated after the period. E2F-1 and DP-1 were expressed from the pMAM-Neo expression vector in the absence of dexamethasone (32).
AML-1 Regulates the G₁ Phase of the Cell Cycle

When AML-1B-expressing cells were assayed, nearly twice as many BrdU-labeled cells expressing AML-1B were re-entering S phase 10 h after labeling as control cells (34% and 30% versus 17% for control cells; Fig. 2B compare panels pMT-AML-1B.7 and pMT-AML-1B.28 with pMT.3 at 10 h). At 12 h post-labeling, nearly 50% more AML-1B-expressing cells were in mid-S phase (45% and 54% S-phase, pMT-AML-1B.7 and pMT-AML-1B.28, respectively; Fig. 2B). In addition, at the 12-h time point, the unlabeled AML-1B-expressing cells showed accelerated cell cycle kinetics (Fig. 2B; note also the unlabeled cells in the 9- and 13-h panels marked with arrowheads in Fig. 2C). 12–13 h after labeling the AML-1B-expressing cells had exited the G₁ phase and were in late S phase (Fig. 2, B and C) (note the reduction in the number of cells in early S phase of the unlabeled cell populations of the plots expressing AML-1B as compared with control and E2F-1-expressing cell plots (Fig. 2B, and marked with brackets Fig. 2C)). Similar results were obtained from more than 10 independently isolated single cell clones that were selected from three different parental populations of 32D.3 cells. The percentages of cells entering S phase 10 or 11 h after BrdU labeling from three different experiments are shown in Table I. Each AML-1B-expressing cell line entered S phase faster than the control cell lines (Fig. 2B and Table I).

The results of DNA content analysis (Fig. 2A) and BrdU analysis of S phase suggested that AML-1B caused accelerated entry into S phase. In principle, this could be due to a shortening of the G₁ or the G₂/M phases. However, DNA content analysis indicated that the total number of AML-1B-expressing cells in the G₂/M phase were similar to control cells, and the number of cells in the G₁ phase was reduced, suggesting a shortening of the G₁ but not G₂/M phases (Fig. 2A). To extend this result and to directly determine whether the G₂/M phase was shortened by AML-1B expression, we used BrdU pulse-chase analysis to determine the time required to traverse G₂/M (Fig. 3 and Table II). This was accomplished by measuring the time required for the first BrdU-labeled cells (those cells in late S phase at the time of labeling) to traverse G₂/M and enter the G₁ phase. Both control G418-resistant cells (pMT) and AML-1B-expressing cells passed through the G₂/M phase and began entering the G₁ phase after 3–4 h (Fig. 3 and Table II). Analysis of further time points confirmed this result. We conclude that enforced expression of AML-1B does not affect G₂/M but shortens the G₁ phase, consistent with the ability of an AML-1 inhibitor to arrest cells in the G₁ phase (28).

AML-1B Cannot Induce G₁ to S Phase Progression in the Absence of Growth Factors—The observation that AML-1B-expressing accelerated S phase entry in myeloid progenitor cells was unexpected. Cell cycle regulatory transcription factors and oncogenes that act in the G₁ phase of the cell cycle such as E2F-1 and c-Myc do not alter the timing of the cell cycle (32, 33, 40). However, both E2F-1 and c-Myc can induce S phase progression of 32D.3 cells in the absence of IL-3 (32, 33, 40). Therefore, we tested whether AML-1B could also induce continued cell cycle progression in the absence of cytokine. Cell lines were cultured in media lacking IL-3 for 12 h, and cell cycle progression was measured using propidium iodide staining to determine their DNA content. E2F-1-expressing cells displayed no apparent cell cycle defects in the presence of IL-3 (Fig. 4). In the absence of IL-3, E2F-1 induced continued S phase entry in the absence of the cytokine (Fig. 4). By contrast, there were fewer cells expressing AML-1B in the G₁ phase and more cells in S-phase in the presence of IL-3, but in the absence of IL-3 these cells accumulated in the G₁ phase (Fig. 4). Thus, AML-1B expression induced accelerated cell cycle progression of the G₁ phase consistent with the ability of an AML-1 inhibitor to arrest cells in the G₁ phase (28).

**Table I**

| Cell linesa | Cells in S phaseb |
|-------------|------------------|
| pMT.10      | 16               |
| 1B.5        | 38               |
| 1B.7        | 47               |
| 1B.27       | 44               |
| 1B.28       | 46               |
| pMT.4       | 38               |
| pMT.10      | 37               |
| 1B.2        | 58               |
| 1B.3        | 49               |
| 1B.6        | 63               |
| 1B.28       | 61               |
| pMT.3       | 27               |
| pMT.4       | 26               |
| 1B.6        | 48               |
| 1B.7        | 49               |
| 1B.32       | 40               |
| 1B.36       | 48               |
| 1B.50       | 41               |

a Cell lines used were 32D.3 clones containing either vector alone (pMT) or vector containing an AML-1B insert (1B).
b Shown are the percentage of cells in S phase at the indicated time (10 or 11 h) after BrdU-labeling.
AML-1 Regulates the G₁ Phase of the Cell Cycle

Determination of G₂/M transit time in 32D.3-overexpressing cell lines

Cells were assayed as described in the legend to Fig. 2A. At the indicated times, the percentage of G₁ cells labeled with BrdU was determined using the ModFit algorithm.

| Cell lines | 0 h | 3 h | 4 h |
|------------|-----|-----|-----|
| 32D.3      | 0   | 0.5 | 5.0 |
| pMT.1      | 0   | 1.0 | 5.2 |
| pMT.3      | 0   | 0.1 | 4.5 |
| 1B.7       | 0   | 0.9 | 4.9 |
| 1B.51      | 0   | 0.7 | 4.2 |

a Cell lines used were 32D.3 clones containing either vector alone (pMT) or vector containing an AML-1B insert (1B).
b Percentage of cells in the G₁ phase at 3 or 4 h after BrdU labeling.

AML-1 Activates Cell Cycle-regulated Promoters—The shortening of the G₁ phase and the higher levels of cyclin D2 suggested that AML-1 might activate key cell cycle regulatory genes that affect cell cycle progression. Therefore, we scanned the promoters for the G₁ cyclins and found several AML-1 binding sites in the cyclin D2 promoter. To determine whether AML-1 could activate the cyclin D2 promoter, we used this promoter linked to a luciferase reporter gene in transient assays. In COS-7 cells, the cyclin D2 promoter was activated by wild-type AML-1B but not by an AML-1B containing a point mutation that ablates DNA binding (L175D, changing residue 175 from leucine to aspartic acid, Fig. 6A). Expression from the internal control promoter was unaffected by AML-1B (data not shown, but used to correct for transfection efficiency). Promoter deletion analysis indicated that 5′ promoter sequences containing several potential and known AML-1 binding sites were required for full AML-1B-dependent transactivation, whereas a perfect AML-1 binding site 3′ to the first transcriptional start site was not sufficient for full activation (Fig. 6B). The caveat in this analysis is that cyclin D2 is regulated during the cell cycle. Thus, the activation observed with AML-1B could be indirect if AML-1B was stimulating cell cycle progression. Therefore, we compared the ability of AML-1B to activate the cyclin D2 promoter with other cell cycle regulated promoters. Although the cyclin D2 promoter was activated to a greater extent than the cyclin D1 or human thymidine kinase promoter (which are not known to contain AML-1 binding sites), these promoters were also activated by AML-1B (Fig. 6C). Once again, the internal control was unaffected by AML-1B (data not shown).

AML-1B Effects on the Cell Cycle Require DNA Binding and Transcriptional Regulatory Domains—Because we could not determine whether AML-1B directly activated cell cycle regulatory promoters, we probed the mechanism of AML-1B cell cycle control by asking whether expression of AML-1a, which
AML-1 Regulates the $G_1$ Phase of the Cell Cycle

AMl-1 is unusual in that it is an oncogene, yet it is disrupted by chromosomal translocations in acute leukemia. We observed that enforced expression of AML-1B induced accelerated S phase entry (Figs. 2 and 7 and Table I). Cultures of cells expressing AML-1B had fewer cells in the $G_1$ phase and more cells in S phase (Fig. 2). The time needed to traverse $G_2/M$ remained constant in these cells (Fig. 3, Table II), which is consistent with expression of AML-1B accelerating transit through the $G_1$ phase of the cell cycle. Thus, AML-1B is one of the first transcription factors described that shortens the length of the $G_1$ phase of the mammalian cell cycle. Furthermore, this work points toward a cell cycle mechanism for the ability of AML-1 to transform cells.

DISCUSSION

The ability of AML-1B to alter the cell cycle led us to examine the promoters of known components of the $G_1$ phase cell cycle control machinery to determine whether any of these genes could be direct targets of AML-1B. We found perfect AML-1B binding sites in the p21Waf1/Cip1 cyclin-dependent kinase inhibitor promoter (16, 43) and the cyclin D2 promoter but not in the E2F1, cdk2, or cdk4 promoters. Increasing amounts of AML-1B or the AML-1B L175D mutant plasmid were co-transfected with 700 ng of pGL2-cyclin D2 plasmid. Fold activation was calculated after correcting for transfection efficiency using a plasmid expressing a secreted form of alkaline phosphatase (SEAP) from the cytomegalovirus IE promoter. The numbers below the bars indicate the amount of the plasmid in nanograms. For the AML-1B 800-ng sample, the internal control was not used, as this level of input plasmid suppressed the expression of SEAP, probably due to promoter competition. The levels shown are the average of duplicate experiments. In those samples lacking error bars, the error was too small to graph. For subsequent experiments, 200–300 ng of AML-1B plasmid was used. B, schematic representation of the murine cyclin D2 promoter and fold activation by AML-1B. A perfect AML-1 binding site is shown as a hatched box, and 5 of 6 base pair matches of the consensus binding site are shown as dark boxes. Numbers above or below each box indicate the number of nucleotides from the first major transcriptional start site. Fold activation is shown on the right hand side. C, AML-1 activates the cyclin D1 and thymidine kinase (TK) promoters. The ability of AML-1B to activate the cyclin D2 promoter was compared with the TK and D1 promoters that lack perfect AML-1 binding sites. Note that both TK and D1 were activated but to a lesser degree than the D2 promoter.
Initially, we observed faster growth of the AML-1B-expressing cells, suggesting that these cells had not compensated for the acceleration of the G1 phase and were cycling faster. However, as these lines were maintained in culture, this phenotype was lost. It is likely that these cells eventually compensated for the shortening of G1 by lengthening the S phase, as has been observed for cells overexpressing the G1 cyclins (29, 30). We also found that the cell culture conditions were critical for revealing the AML-1B-cell cycle phenotype. For instance, at high cell densities, the shortening of G1 was lost (data not shown), suggesting density-dependent effects. The mechanisms behind these phenotypes will require further investigation.

Transcription factors such as E2F-1 and c-Myc are capable of affecting cellular proliferation, but enforced expression of these factors did not affect the timing of the 32D.3 cell cycle (32, 40). Therefore, the phenotype of enforced AML-1B expression is more similar to that of overexpression of the G1 cyclins, accelerating the G1 phase without affecting the entry to or exit from quiescence (29–31). Although stimulation of cyclin D2 or p21Waf1/Cip1 expression may contribute to AML-1B-mediated G1 phase control, these genes are unlikely to be the only mediators of this phenotype. We are actively searching for other cell cycle control genes that may contribute to AML-1-cell cycle control.

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