The promyelocytic leukemia RARα target gene encoding an adaptor molecule-1 (PRAM-1) is involved in a signaling pathway induced by retinoic acid in acute promyelocytic leukemia (APL) cells. To better understand the function of PRAM-1, we have undertaken the identification of its partners through a yeast two-hybrid screen. Here, we show that the proline-rich domain of PRAM-1 interacted with the Src homology 3 (SH3) domain of hematopoietic progenitor kinase 1 (HPK-1)-interacting protein of 55 kDa (HIP-55, also called SH3P7 and Abp1) known to stimulate the activity of HPK-1 and c-Jun N-terminal kinase (JNK). Overexpression of PRAM-1 in the NB4 APL cell line increased arsenic trioxide-induced JNK activation through a caspase 3-like-dependent activity. Dissociation of the SH3 domain from the rest of the HIP-55 protein was observed in the NB4 APL cell line treated with arsenic trioxide due to specific cleavage by caspase 3-like enzymes. The cleavage of HIP-55 correlated with the induction of PRAM-1 mRNA and protein expression. Taken together, our results suggest that the caspase 3-cleaved SH3 domain of HIP-55 is likely involved in PRAM-1-mediated JNK activation upon arsenic trioxide-induced differentiation of NB4 cells.

Acute promyelocytic leukemia (APL) is associated with five reciprocal translocations always involving the retinoic acid receptor α (RARα) (1, 2). In more than 95% of APL, the specific translocation t(15;17) produces the PML-RARα and RARα-PML fusion proteins (3). The association of histone deacetylases with PML-RARα has been described in APL cells (4–6). PML-RARα would therefore recruit a histone deacetylase complex to RA response elements leading to the repression of RA target genes critical to myeloid differentiation. The dissociation of the histone deacetylase complex from the fusion protein is obtained by treating cells with pharmacological concentrations of RA, which could explain the sensitivity of APL cells to RA (4–6). When treated with RA, these cells can withdraw from the cell cycle and undergo terminal maturation both in vitro (7) and in vivo (8–10). This suggests a molecular mechanism by which RA-responsive genes critical to myeloid differentiation are repressed in leukemia cells and de novo induced when these cells are treated with RA (7, 8). Arsenic trioxide (As2O3) has been identified as an alternative therapy in patients with both RA-sensitive and RA-resistant APL (9, 10). As2O3 triggers apoptosis and differentiation of APL cells both in vitro and in vivo (10, 11). Indeed, PML-RARα-bound co-repressors are released from DNA upon As2O3 treatment of APL cells, leading to the activation of PML-RARα target genes through PML-RARα degradation (12).

To identify genes controlling proliferation and/or induced differentiation of both normal and leukemia cells, we have used a differential screening strategy to isolate genes that are activated during induced maturation of APL cells (13). Among four novel genes, PRAM-1 (PML-RARα target gene encoding an adaptor molecule-1) is a first example of an adaptor in which expression is inhibited and superinduced when PML-RARα is expressed alone and in the presence of RA, respectively (14). PRAM-1 shares structural homologies with SLAP-130 (SLP-76-associated protein of 120 kDa)/FYB (Fyn-binding protein) re-named ADAP (adhesion- and degranulation-promoting adaptor protein) (15, 16), which is involved in clonal expansion of activated T-cells through transcriptional regulation of the IL2 gene (17, 18), mastocyte degranulation (19), as well as integrin-mediated adhesion (20, 21). PRAM-1 interacts with several signaling intermediates, such as the SLP-76 and SKAP55-HOM adaptors and the Src tyrosine kinase LYN (14).

Hematopoietic progenitor kinase-1 (HPK-1), a hematopoietic-specific mitogen-activated protein 4 kinase, is an upstream activator of c-Jun N-terminal kinase (JNK) involved in T-cell receptor signaling (22–25). HPK-1-interacting protein of 55 kDa (HIP-55, also called Abp1 and SH3P7) has an actin-binding domain at its N terminus and an SH3 domain at its C terminus (26–28). HIP-55 mediates HPK-1 and JNK activation (26, 29). It is recruited to the immunological synapse and regulates T-cell receptor signaling (30). HIP-55 is also involved in receptor-mediated endocytosis (31, 32). HIP-55 is cleaved by caspase 3-like enzymes during apoptosis leading to the dissociation of its actin-binding domain from its SH3 domain (33).
To decipher PRAM-1 mechanism of action, we have undertaken the identification of its partners through a yeast two-hybrid screen. Here we show that the proline-rich domain of PRAM-1 interacts with the SH3 domain of HIP-55. Dissociation of the SH3 domain from the rest of the HIP-55 protein was found in NB4 APL cells treated with As$_2$O$_3$ due to a specific cleavage by caspase 3-like enzymes. We show that PRAM-1 mRNA and protein expressions were induced in As$_2$O$_3$-treated NB4 cells. Furthermore, overexpression of PRAM-1 in NB4 cells potentiated As$_2$O$_3$-induced JNK activation.

MATERIALS AND METHODS

Cell Lines, Culture, and Differentiation—NB4 cells (34) were cultured in RPMI 1640 medium (Invitrogen) with 10% fetal bovine serum (PAA Laboratories), 2 mM glutamine and 1% penicillin-streptomycin (Invitrogen). The COS-7 cell line was grown in Petri dishes in Dulbecco’s modified Eagle’s medium supplemented with 5% fetal bovine serum and antibiotics. Exponentially grown NB4 cells were seeded at 2 × 10$^5$ cells/ml 16 h prior to As$_2$O$_3$ (ICN) treatment. Cell differentiation was determined by: (i) the percentage of nitro blue tetrazolium (Sigma)-positive cells and (ii) morphological changes on cytospin slides stained with May-Grunwald-Giemsa (WVF Scientific). For the caspase inhibition, cells were preincubated for 30 min with Z-DEVD-fmk (Calbiochem) before As$_2$O$_3$ treatment.

Plasmid Constructs—The PRAM-1 coding sequence was subcloned into the pGBK7 (Clontech) and into a pSG5 (35)-derived vector to direct the expression of PRAM-1. The PRAM-1 (-183–613) mutant was generated by the internal PvuII fragment deletion. The full-length PRAM-1 cDNA was subcloned into the pBabe retroviral vector (36). The human HIP-55 open reading frame was obtained by PCR amplification using bone marrow cDNA and subcloned into: (i) a pSG5-derived vector to direct the expression of HIP-55 fused to the FLAG epitope at its amino terminus (pSG5FN-HIP-55) and (ii) pGST, a derivative of pGEX-3X, in-frame with the glutathione S-transferase (GST) sequence. Constructs encoding the SH3 domain of HIP-55 (362–430) were amplified by PCR. The hemagglutinin-tagged HIP-55 (pDGK-HIP-55) expression vector was a gift from Dr. F. Kiefer (23). The pGST-c-Jun-(1–223) was a gift from Dr. B. Chotton. Construction of the pSG5FN-HIP-55D361A mutated vector was achieved using the QuickChange site-directed mutagenesis kit (Stratagene). For this, we used a mutated oligonucleotide sequence as indicated in boldface: D361A, 5'-ACACCACATTC-3'. All constructs were verified by oligonucleotide sequence as indicated in boldface: D361A, 5'.
washing buffer (50 mM Tris-HCl, pH 7.5, 100 mM NaCl, 10 mM MgCl2, 0.3 mM dithiothreitol, 5% glycerol, 0.1% Nonidet P-40), the proteins were recovered in Laemmli buffer, separated by SDS-polyacrylamide gel electrophoresis and analyzed by Coomassie staining or autoradiography of dried gels.

**Protein Cleavage Assay**—Recombinant HIP-55 proteins were incubated in 50 µl of caspase reaction buffer (10 mM HEPES, 100 mM NaCl, 10 mM dithiothreitol, 1 mM EDTA, 0.1% CHAPS, pH 7.2) with 100 ng of recombinant caspase 3 (Calbiochem) at 37 °C. The reaction was terminated by adding Laemmli buffer and a 2-min boiling. The samples were resolved by SDS-polyacrylamide gel electrophoresis and analyzed by Western blot.

**Northern Blots**—Total RNA extraction and hybridization were as described previously (14, 37). The HIP-55 probe corresponded to the HIP-55 coding sequence.

**Western Blots,** Antibodies—Western blot analyses were carried out as described previously (14, 37). The HIP-55 antibody revealed the decrease of full-length HIP-55 and the expanded for further analysis.

**RESULTS**

**PRAM-1 Interacted with the SH3 Domain of HIP-55**—In an attempt to identify binding partners for PRAM-1, a yeast two-hybrid screen was used with full-length PRAM-1 as a bait, together with a cDNA library from human bone marrow cells. Four independent clones were recovered: two corresponding to the full-length SKAP-55HOM coding sequence (40, 41) and two to part of HIP-55 (26, 27). The region covered by the two identical HIP-55 clones corresponded to amino acids 65–430 containing two tyrosine-based motifs, a caspase 3 recognition site, and a C-terminal SH3 domain (Fig. 1A) (26, 27, 33). The yeast AH109 strain was then transformed with SKAP-55HOM, HIP-55, or the pACT2 empty plasmid together with the PRAM-1 bait plasmid and grown onto selective media. As shown in Fig. 1B, SKAP-55HOM and HIP-55 cDNAs were found to specifically interact with PRAM-1 in yeast. A specific interaction between PRAM-1 and SKAP-55HOM was also found in myeloid cells (14). We examined therefore the *in vitro* binding of HIP-55 to PRAM-1. Affinity-purified GST and GST-HIP-55 proteins expressed in *E. coli* were incubated with *in vitro* translated PRAM-1 and HPK-1 proteins. As shown in Fig. 1C, PRAM-1 and HPK-1 did associate with both GST-HIP-55 and GST-HIP-55(362–430) containing the SH3 domain but not with the GST alone. Deletion of type I and II SH3 recognition motifs within the PRAM-1 protein abolished PRAM-1 binding to the HIP-55 SH3 domain (Fig. 1D). Altogether, our results indicate that the SH3 domain of HIP-55 can associate with PRAM-1 through the proline-rich domain of PRAM-1.

Because cleavage of HIP-55 by caspase 3 during apoptosis dissociated its SH3 domain from its actin-binding domain (33), we determined whether HIP-55 could be cleaved in response to As2O3 in NB4 cells. Western blot analysis using an anti-HIP-55 antibody revealed the decrease of full-length HIP-55 and the
PRAM-1 (NB4/PRAM-1.1 and 2) or eGFP (NB4/eGFP.1 and 2) as controls were either untreated or treated with 1 or 2 μM As2O3. HPK-1 (26, 29) suggested that PRAM-1 was involved in As2O3—induced activation of the JNK kinase. The fact that HIP-55 is a modulator of PRAM-1 is a novel adaptor molecule likely to be involved in an RA-signaling pathway, and we have reported the association between PRAM-1, LYN, SLP-76, and SKAP55-HOM in RA-treated NB4 cells (14). Here, we have reported that the proline-rich domain of PRAM-1 interacted with the SH3 domain of the HIP-55 adaptor. HIP-55 was originally identified as an HPK-1-like enzyme(s) (Fig. 2C). Mutation of the aspartic acid at position 361 to an alanine residue in HIP-55 protein abrogated its cleavage by caspase 3 (Fig. 2C), indicating that the EHID361 motif of HIP-55 is the caspase 3-specific cleavage site. Altogether, these results strongly suggest that caspase 3 is likely to mediate cleavage of HIP-55 in NB4 cells treated with As2O3.

Overexpression of PRAM-1 in NB4 Cells Potentiated As2O3—induced JNK Activation—Increased PRAM-1 mRNA and protein expression occurred 6 and 12 h, respectively, after exposure of NB4 cells to As2O3 (Fig. 3A), which induced apoptosis with partial granulocytic differentiation (data not shown). Dose-response studies with As2O3-treated cells showed that 24 h of treatment with 2 μM As2O3 induced peak levels of the PRAM-1 protein, which correlated with the cleavage of HIP-55 (Fig. 3B). Furthermore, this also correlated with JNK kinase activation as revealed by an in vitro kinase assay (Fig. 4A). To determine whether PRAM-1 was involved in the activation of JNK by As2O3, NB4 cells were stably transfected with a vector encoding PRAM-1 or eGFP as a control and treated with 2 μM As2O3 (Fig. 4B). Whereas the different pools of cells transfected with either vector showed a cleavage of HIP-55 in response to As2O3, overexpression of PRAM-1 resulted in a higher activation of the JNK kinase. The fact that HIP-55 is a modulator of HPK-1 (26, 29) suggested that PRAM-1 was involved in As2O3—induced activation of the JNK kinase in NB4 cells, likely through its interaction with the SH3 domain of HIP-55 released upon caspase 3 cleavage. To test this hypothesis, NB4 cells were pretreated with the Z-DEVD-fmk caspase inhibitor before As2O3 treatment. As shown in Fig. 5, the caspase inhibitor, which suppressed the cleavage of pro-caspase 3, also suppressed the cleavage of HIP-55 and abolished PRAM-1-mediated activation of JNK (Fig. 5A). This had no effect on As2O3—induced apoptosis as assessed through cell viability (Fig. 5B) and PARP cleavage (Fig. 5C). These results indicated that the stimulation of As2O3—induced JNK activity by PRAM-1 was dependent upon caspase 3 activation. Altogether, our results lend further support to the idea that the SH3 domain of HIP-55 resulting from the cleavage of HIP-55 by caspase 3 is involved in PRAM-1-mediated JNK activation upon As2O3—induced differentiation of NB4 cells.

DISCUSSION

Retinoic acid and arsenic trioxide induce clinical remission of patients with APL with t(15; 17) translocation. Indeed, PML-RARα-bound co-repressors are released from DNA upon both RA and As2O3 treatment of APL cells leading to the activation of genes repressed by PML-RARα (12). This suggested that genes induced in common by RA and As2O3 are likely to be involved in induced myeloid differentiation (42). We found that PRAM-1 is repressed by PML-RARα and induced by RA (14) and As2O3, suggesting that PRAM-1 is likely to be one of these genes.

PRAM-1 is a novel adaptor molecule likely to be involved in an RA-signaling pathway, and we have reported the association between PRAM-1, LYN, SLP-76, and SKAP55-HOM in RA-treated NB4 cells (14). Here, we have reported that the proline-rich domain of PRAM-1 interacted with the SH3 domain of the HIP-55 adaptor. HIP-55 was originally identified as an HPK-1-interacting protein (26). HPK-1 was shown to activate the JNK kinase pathway (22) and to function as a negative regulator for T-cell receptor-mediated AP-1 activation (25). Upon stimulation of the T-cell receptor, HIP-55 was shown to activate HPK-1 or other upstream kinases, which, in turn, activate the JNK kinase (29). SLP-76, SKAP55-HOM, and HIP-55 are essential components of T-cell receptor-signaling cascades regulating gene transcription, T-cell receptor and integrin clustering, endocytosis, and actin reorganization. The fact that PRAM-1 interacts with the SH3 domain of HIP-55 reinforces the view that PRAM-1 and ADAP may occupy a similar functional niche. Furthermore, in NB4 cells, overexpression of PRAM-1 potentiated As2O3—induced JNK activation.

Cleavage of HIP-55 during apoptosis induced by Fas liga-
Caspass 3 was also shown to be involved in the phorbol ester-induced differentiation of U937 cells in the absence of cell death (46). We showed that, in NB4 cells treated with As$_2$O$_3$, the Z-DEVDFMK caspase inhibitor suppressed cleavage of HIP-55 as well as PRAM-1-mediated activation of JNK without affecting cell death. Considering that in our present observation, PRAM-1 interacted with the SH3 domain of HIP-55 and potentiated As$_2$O$_3$-induced JNK activation together with the well established fact that HIP-55 mediated JNK activation upon T-cell receptor stimulation (26, 29), it is tempting to speculate that the SH3 domain of HIP-55 resulting from the caspase 3 cleavage of HIP-55 is involved in PRAM-1-mediated JNK activation. This will have to be further investigated.

The fact that PRAM-1 is an adaptor molecule involved in both RA- and As$_2$O$_3$-signaling pathways suggests that PRAM-1 may be central to molecular complexes important for maturation of APL cells. The formation of such a complex may reactivate a normal signaling pathway that might be interrupted in leukemia cells.

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**FIG. 5.** The Z-DEVDFMK caspase inhibitor suppressed the cleavage of HIP-55 and abolished PRAM-1-mediated activation of JNK in As$_2$O$_3$-treated NB4 cells. NB4/eGFP.1 and NB4/PRAM-1.1 cells were either untreated (−) or pretreated (+) with 40 μM of Z-DEVDFMK prior to a 2 μM As$_2$O$_3$ treatment for 24 h, as indicated (A–C). Figure is representative of four experiments showing the cleavage of pro-caspase 3, the expression of PRAM-1, HIP-55, and JNK activity (A), the number of viable cells (B), and the cleavage of PARP (C). Protein extracts from 10$^5$ cells were separated by SDS-PAGE and immunoblotted for PRAM-1 and HIP-55. In *vitro* kinase assays were performed as described in the legend to Fig. 4. Cell viability was estimated using standard trypan blue dye exclusion assay. Cleavage of PARP and pro-caspase 3 was assessed by Western blot using anti-PARP and anti-caspase 3 antibodies. Representative results from at least two experiments are shown.
JNK Activation by PRAM-1

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PRAM-1 Potentiates Arsenic Trioxide-induced JNK Activation
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